Optimisation des interactions patient-ventilateur en ventilation assistée : intérêt des nouveaux algorithmes de ventilation

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THÈSE

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Optimisation des interactions patient-ventilateur en ventilation assistée : Intérêt des nouveaux algorithmes de ventilation

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RESUME

En ventilation assistée, les interactions patient-ventilateur, qui sont associés au pronostic, dépendent pour partie des algorithmes de ventilation.

Objectifs: Caractériser l'intérêt potentiel des nouveaux algorithmes de ventilation dans l'optimisation des interactions patient-ventilateur: 1) en ventilation invasive, deux modes et leurs algorithmes nous ont semblé novateurs et nous avons cherché à personnaliser l'assistance du ventilateur en fonction de l'effort respiratoire du patient au cours de ces modes proportionnels: ventilation assistée proportionnelle (PAV+) et ventilation assistée neurale (NAVA) ; 2) en ventilation non-invasive (VNI) nous avons évalué si les algorithmes VNI des ventilateurs de réanimation et des ventilateurs dédiés à la VNI diminuaient l'incidence des asynchronies patient-ventilateur.

Méthodes : 1) En PAV+ nous avons décrit un moyen de recalculer le pic de pression musculaire réalisée par le patient à chaque inspiration à partir du gain réglé et de la pression des voies aériennes monitorée par le respirateur. Nous avons alors évalué la faisabilité clinique d'ajuster l'assistance en ciblant un intervalle jugé normal de pression musculaire. 2) Nous avons comparé une titration de l'assistance en NAVA et en aide inspiratoire (AI) en se basant sur les indices d'effort respiratoire. 3 et 4) En VNI, nous avons évalué l'incidence des asynchronies patient-ventilateur avec et sans l'utilisation d'algorithmes VNI : sur banc d'essai au cours de conditions expérimentales reproduisant la présence de fuites autour de l'interface ; en clinique chez des patients de réanimation.

Résultats : En PAV+, ajuster le gain dans le but de cibler un effort respiratoire normal était faisable, simple et souvent suffisant pour ventiler les patients depuis le sevrage de la ventilation mécanique jusqu'à l'extubation. En NAVA, l'analyse des indices d'effort respiratoire a permis de préciser les bornes d'utilisation et de comparer les interactions patient-ventilateur avec l'AI dans des intervalles d'assistance semblables. En VNI, nos données pointaient l'hétérogénéité des algorithmes VNI sur les ventilateurs de réanimation et retrouvaient une meilleure synchronisation patient-ventilateur avec l'utilisation de ventilateurs dédiés à la VNI pour des qualités de pressurisation par ailleurs identiques.

Conclusions : En ventilation invasive, personnaliser l'assistance des modes proportionnels optimise les interactions patient-ventilateur et il est possible de cibler une zone d'effort respiratoire normale en PAV+. En VNI, les ventilateurs dédiés améliorent la synchronisation patient-ventilateur plus encore que les algorithmes VNI sur les ventilateurs de réanimation, dont l'efficacité varie grandement selon le ventilateur considéré.

TITLE Patient-ventilator interactions optimization: new ventilation algorithms contribution

ABSTRACT

During assisted mechanical ventilation, patient-ventilator interactions, which are associated with outcome, partly depend on ventilation algorithms.

Objectives: : 1) during invasive mechanical ventilation, two modes offered real innovations and we wanted to assess whether the assistance could be customized depending on the patient's respiratory effort during proportional ventilatory modes: proportional assist ventilation with load-adjustable gain factors (PAV+) and neurally adjusted ventilator assist (NAVA); 2) during noninvasive ventilation (NIV): to assess whether NIV algorithms implemented on ICU and dedicated NIV ventilators decrease the incidence of patient-ventilator asynchrony.

Methods: 1) In PAV+ we described a way to calculate the muscle pressure value from the values of both the gain adjusted by the clinician and the airway pressure. We then assessed the clinical feasibility of adjusting the gain with the goal of maintaining the muscle pressure within a normal range. 2) We compared titration of assistance between neurally adjusted ventilator assist (NAVA) and pressure support ventilation (PSV) based on respiratory effort indices. During NIV, we assessed the incidence of patient-ventilator asynchrony with and without the use of NIV algorithms: 1) using a bench model; 2) and in the clinical settings.

Results: During PAV+, adjusting the gain with the goal of targeting a normal range of respiratory effort was feasible, simple, and most often sufficient to ventilate patients from the onset of partial ventilatory support until extubation. During NAVA, the analysis of respiratory effort indices allowed us to precise the boundaries within which the NAVA level should be adjusted and to compare patient-ventilator interactions with PSV within similar ranges of assistance. During NIV, our data stressed the heterogeneity of NIV algorithms implemented on ICU ventilators. We therefore reported that dedicated NIV ventilators allowed better patient-ventilator synchronization than ICU ventilators, even with their NIV algorithms engaged.

Conclusions: During invasive mechanical ventilation, customizing the assistance during proportional ventilatory modes with the goal of targeting a normal range of respiratory effort optimizes patient-ventilator interactions and is feasible with PAV+. During NIV, dedicated NIV ventilators allow better patient-ventilator synchrony than ICU ventilators, even with their NIV algorithm engaged. ICU ventilators' NIV algorithms efficiency is however highly variable among ventilators.

Mots clés :

Ventilation assistée ; Ventilation assistée proportionnelle ; Ventilation assistée neurale ; Pression musculaire ; Ventilation non-invasive ; Algorithme VNI ; Interaction patient-ventilateur ; Asynchronie patient-ventilateur

Keywords:

Assisted mechanical ventilation; Proportional assist ventilation; Neurally adjusted ventilatory assist; Muscle pressure; Noninvasive ventilation; NIV algorithm; Patient-ventilator interaction; Patient-ventilator asynchrony

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ABBREVIATIONS

- **%assist** : pourcentage d'assistance
- **Ccw** : compliance de la paroi thoracique
- **Crs** : compliance du système respiratoire
- **EAdi** : activité électrique du diaphragme
- **EMG** : électromyogramme
- **IA** : index d'asynchronie
- **NAVA** : neurally adjusted ventilatory assist
- **PAV+** : proportional assist ventilation with load-adjustable gain factors
- **Paw**: pression des voies aériennes
- $\mathbf{P_{aw,Peak}}$: pic de pression des voies aériennes
- **Pcw** : pression de rétraction élastique de la paroi thoracique
- **Pdi** : pression transdiaphragmatique
- **PEP** : pression expiratoire positive
- **PEPi** : PEP intrinsèque
- **Pes** : pression œsophagienne
- **Pga** : pression gastrique
- **Pmus** : pression musculaire des muscles respiratoires
- $\mathbf{P_{mus,Peak}}$: pic de pression musculaire des muscles respiratoires
- **Ptot** : pression totale
- **PTPdi** : produit pression-temps diaphragmatique
- **PTPes** : produit pression-temps œsophagien
- **Rrs** : résistances du système respiratoire
- **Te** : temps expiratoire
- **Ti** : temps inspiratoire
- **V** : volume
- **V'** : débit des voies aériennes
- **VAC** : ventilation assistée contrôlée
- **VNI** : ventilation non invasive
- **VSAI** : ventilation spontanée avec aide inspiratoire
- **WOB** : travail respiratoire (« work of breathing »)

SOMMAIRE

1. ETAT DES CONNAISSANCES

1.1. Introduction aux interactions patient-ventilateur

Au cours de la ventilation mécanique dite assistée, le patient déclenche tous les cycles délivrés par le ventilateur (1). Les principaux objectifs d'une telle ventilation sont d'assurer l'hématose tout en diminuant l'effort respiratoire du patient afin, idéalement, de le maintenir dans des valeurs normales (1-6). Ses principaux avantages sur la ventilation contrôlée sont de limiter les lésions diaphragmatiques induites par la ventilation mécanique (7-13), de diminuer le niveau de sédation (14-16), de favoriser la mobilisation précoce (17, 18), et ainsi la conduite du sevrage de la ventilation mécanique. La ventilation assistée représente ainsi la majorité du temps de ventilation en ventilation invasive (19, 20), et bien évidemment la totalité du temps en ventilation non-invasive (VNI).

Entre un patient qui respire spontanément et un ventilateur qui assiste chacun de ses efforts inspiratoires, le concept d'interactions patient-ventilateur comprend à la fois la notion de synchronisation entre l'insufflation du ventilateur et l'inspiration du patient et la notion d'adéquation entre le niveau d'assistance et les besoins du patient en termes d'effort respiratoire (1, 3, 4). Ces interactions dépendent du patient lui-même (pathologie respiratoire, cardiaque, neurologique sous-jacente, affection aiguë ayant nécessité le recours à la ventilation mécanique, coopération du patient…), et bien sûr du ventilateur (algorithme d'asservissement du mode ventilatoire, algorithmes supplémentaires en cas de fuites, qualité technologique…), et des réglages qu'en fait le clinicien. Par ailleurs il existe une interrelation entre les différents composants des interactions patient-ventilateur. Par exemple la sur-assistance peut affecter la synchronisation patient-ventilateur (21, 22). La qualité des interactions patient-ventilateur peut ainsi se juger par l'analyse de la synchronisation patient-ventilateur et la quantification de l'effort respiratoire du patient – qui constituent donc des

cibles thérapeutiques de choix dans l'optimisation des interactions patient-ventilateur – mais aussi par le comportement respiratoire qui en résulte ainsi que le respect de sa variabilité naturelle (23).

1.1.1. La synchronisation patient-ventilateur

La synchronisation patient-ventilateur fait référence à la synchronisation temporelle entre l'assistance délivrée par le ventilateur et l'effort inspiratoire du patient (1, 3, 4). Les pertes de synchronisation entre l'insufflation du ventilateur et l'effort inspiratoire du patients sont ainsi appelées « asynchronies patient-ventilateur ». Différentes asynchronies – qui ont chacune des origines physiopathologiques propres qui seront détaillées plus loin – ont été rapportées selon les différents scénarios possibles (Fig.1): l'effort inefficace, l'auto-déclenchement, l'insufflation prolongée, le cycle court, le double déclenchement (22, 24).

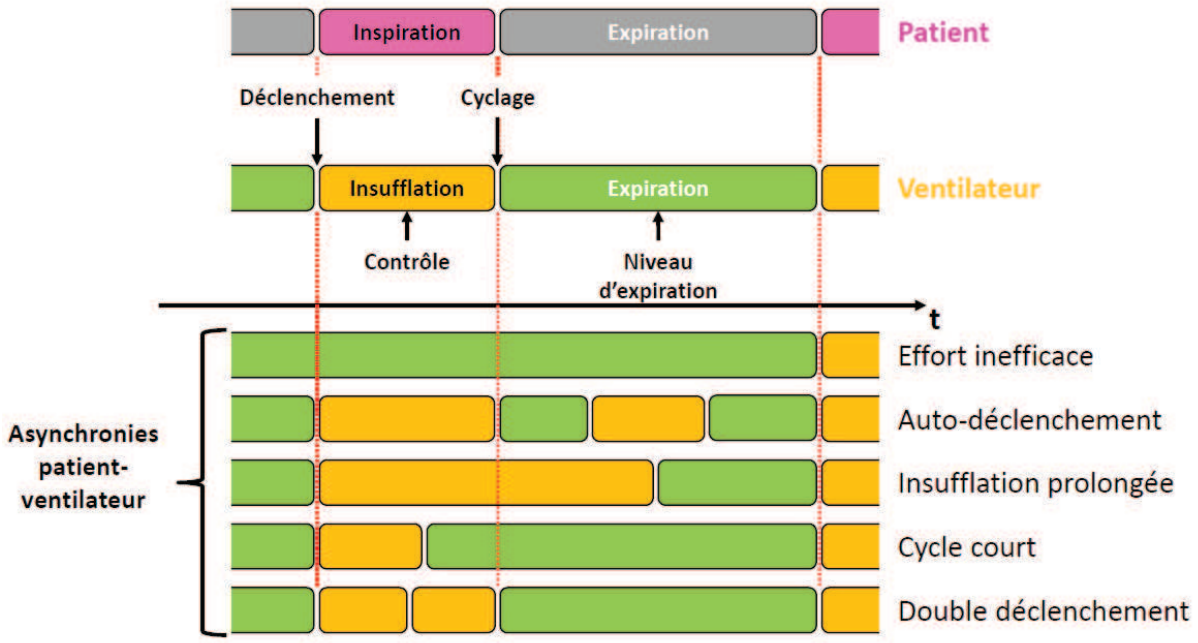

Figure 1 Représentation schématique des principales asynchronies patient-ventilateur. En haut est représenté un cycle respiratoire spontané du patient ainsi qu'un cycle du ventilateur au cours d'une synchronisation théorique parfaite. Sous l'échelle de temps sont représentées les insufflations du ventilateur au cours des principales asynchronies patient-ventilateur.

L'incidence globale des asynchronies patient-ventilateur est généralement mesurée par l'index d'asynchronie (*IA*), qui représente le pourcentage de cycles asynchrones et se calcule ainsi (22, 24):

$$IA\ (\%) = \frac{nombre\ d'asynchronies}{efforts\ inefficaces + cycles\ délivrés\ par\ le\ ventilateur} \times 100$$

1.1.2. L'effort respiratoire du patient

L'un des principaux objectifs de la ventilation assistée est de prendre en charge une partie de l'effort respiratoire du patient afin de le maintenir dans une zone normale ou acceptable (1-6). La mesure d'un indice d'effort fiable au lit du malade n'est cependant pas encore disponible en routine, rendant l'adaptation des réglages du ventilateur difficile et potentiellement dangereux pour le patient. En effet, la mesure quantitative de l'effort inspiratoire du patient nécessite la mise en place d'une sonde œsophagienne à simple ou double ballonnet afin de mesurer la pression œsophagienne (*Pes*), ainsi que la pression gastrique (*Pgas*) en cas de double ballonnet. La pression œsophagienne représente une approximation correcte de la pression pleurale (25, 26). Les mesures de pressions œsophagienne et gastrique permettent ainsi de calculer les principaux indices d'effort respiratoire (27-30) (Fig. 2):

- La pression trans-diaphragmatique (*Pdi*):

$$Pdi = Pga - Pes$$

  et son produit pression-temps (*PTPdi*) :

$$PTPdi = \int Pdi.dt$$

- La pression musculaire, qui est la différence entre la pression de rétraction élastique de la paroi thoracique (*Pcw*) et la pression œsophagienne :

$$Pmus = Pcw - Pes$$

La *Pcw* dépend du volume et de la compliance de la paroi (*Ccw*):

$$Pcw = \frac{V}{Ccw}$$

Ainsi, la pression musculaire peut s'écrire ainsi :

$$Pmus = \frac{V}{Ccw} - Pes$$

- Le travail respiratoire (appelé « work of breathing » ou *WOB*):

  En physique, le travail représente le produit d'une force et d'un déplacement. Une force étant le produit d'une pression et d'une surface, et un déplacement un volume divisé par une surface, en physiologie respiratoire, le travail respiratoire correspond à l'aire comprise dans la courbe Pression musculaire-Volume (V) au cours d'un cycle respiratoire :

$$WOB = \int Pmus \times V$$

- Le produit pression-temps œsophagien (*PTPes*), qui correspond à l'aire sous la courbe de la pression musculaire en fonction du temps:

$$PTPes = \int Pmus.dt$$

La *Pdi* et le *PTPdi* représentent essentiellement l'effort réalisé par le diaphragme. En cas de participation importante des muscles respiratoires accessoires, ils ne peuvent représenter qu'une portion de l'effort inspiratoire. Il existe peu de données concernant les valeurs normales de *Pmus* (29). En revanche, le *WOB* et le *PTPes* sont des mesures plus largement validées de l'effort respiratoire (2, 27, 28, 30-37). Le *PTPes* a l'avantage sur le *WOB* de comptabiliser aussi les efforts iso-volumiques ou inefficaces. En effet, si aucun volume n'est généré par un effort inspiratoire, comme au cours d'un effort inefficace en ventilation assistée, le *WOB* est nul alors que le *PTPes* comptabilise l'intensité de cet effort. Mancebo et coll. ont rapporté chez des sujets sains une valeur de *PTPes* de 86 ± 21 cm $H_2O.s.min^{-1}$ (37).

Par ailleurs, au cours d'une épreuve de sevrage de la ventilation mécanique réussie, Jubran et Tobin retrouvait un *PTPes* inférieur à 200 cm $H_2O.s.min^{-1}$ (35). Ainsi, un *PTPes* compris entre 50 et 150 cm $H_2O.s.min^{-1}$ peut être considéré comme un effort respiratoire normal et pourrait constituer une cible thérapeutique au cours de la ventilation assistée (27).

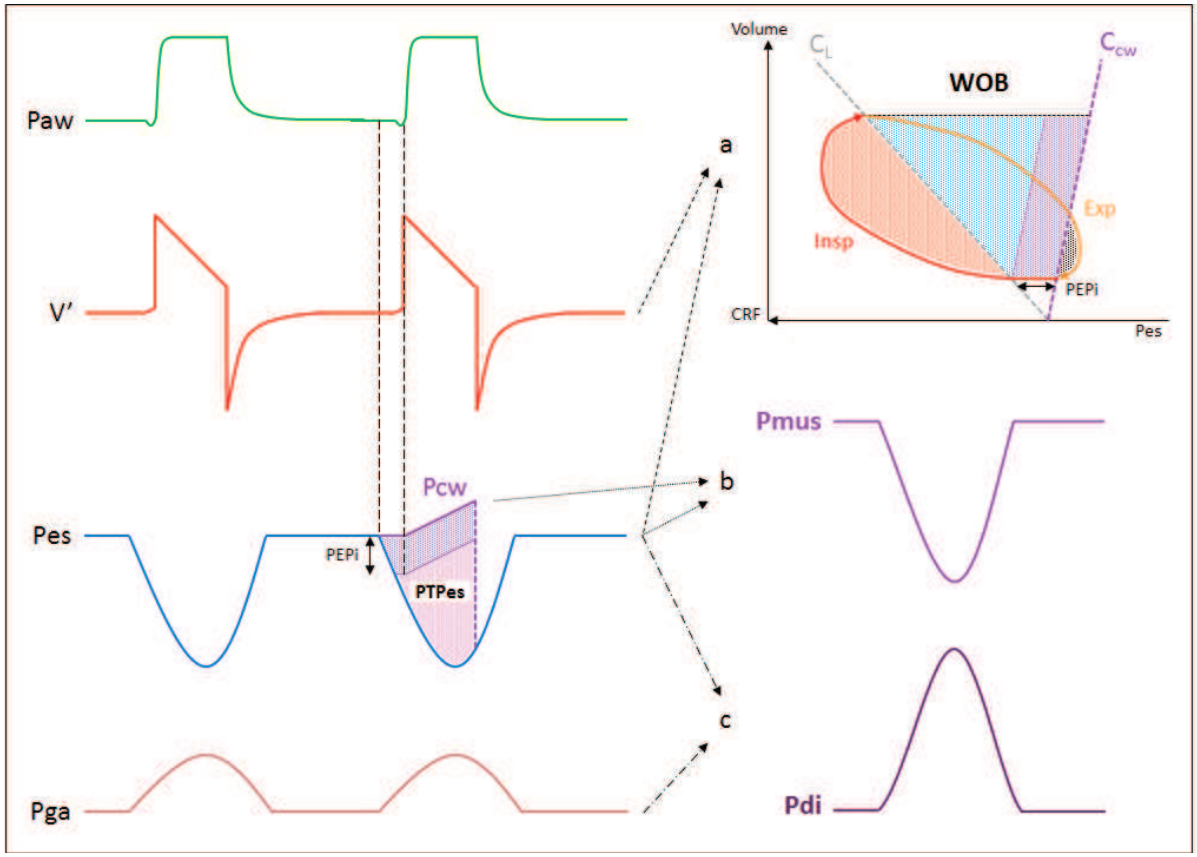

Figure 2 Calcul des principaux indices d'effort respiratoire. La partie gauche de la figure représente de haut en bas les courbes de pression des voies aériennes (*Paw*), de débit des voies aériennes (*V'*), de pression œsophagienne (*Pes*) et de pression gastrique (*Pga*) théoriques en VSAI chez un patient ayant une *PEP* intrinsèque (*PEPi*). Les signaux de débit des voies aériennes et de pression œsophagienne permettent de tracer la relation pression-volume (le volume étant obtenu par intégration du signal de débit) et ainsi de calculer le travail respiratoire ou *WOB* (schéma a, voir texte pour la formule). Le *WOB* peut être partitionné en *WOB* résistif (aire rouge), élastique (aire comprise en les courbes de compliance de la paroi thoracique [C_{cw}] et du poumon [C_L] : aires bleue et aire violette, cette dernière étant liée à l'existence d'une *PEPi*), et expiratoire (aire grise) en cas d'expiration active. La pression musculaire (*Pmus*, schéma b) se calcule comme la différence entre la pression de rétraction élastique de la paroi thoracique (*Pcw*) et la *Pes*. La pression transdiaphragmatique (*Pdi*, schéma c) représente la différence entre la pression gastrique (*Pga*) et la *Pes*. Le produit pression-temps œsophagien (*PTPes*) correspond à l'aire sous la courbe de la *Pmus* en fonction du temps, l'effort lié à la *PEPi* est représenté par l'aire plus foncée.

1.2. Interactions patient-ventilateur au cours des modes classiques de ventilation assistée

1.2.1. Interactions patient-ventilateur au cours de la ventilation assistée contrôlée

Au cours de la ventilation assistée contrôlée (VAC), le clinicien règle un volume courant et une fréquence respiratoire. D'un point de vue technologique, délivrer un volume courant correspond à délivrer un débit d'insufflation pendant le temps nécessaire pour atteindre le volume de consigne. En conditions passives, la valeur de la pression dans les voies aériennes dépend alors du débit d'insufflation et du volume insufflé, ainsi que de la mécanique respiratoire du patient, selon l'équation suivante, appelée équation de mouvement du système respiratoire (38):

$$Paw_{(t)} = P_0 + Rrs \times V'_{(t)} + \frac{V_{(t)}}{Crs}$$

où : *Paw* est la pression dans les voies aériennes, P_0 la pression de départ (en pratique il s'agit de la PEP totale), *Rrs* les résistances du système respiratoire, *V'* le débit dans les voies aériennes, *V* le volume et *Crs* la compliance du système respiratoire. Lorsque le patient fait un effort respiratoire spontané en VAC, le ventilateur délivre un cycle supplémentaire. La VAC réglée avec une fréquence respiratoire inferieure à la fréquence du patient peut donc être utilisée comme mode de ventilation assistée. Cependant, lorsque le patient inspire spontanément, le débit d'insufflation reste identique puisqu'il s'agit de la consigne donnée au ventilateur au cours de ce mode. Ainsi, on observe un creusement de la courbe de *Paw* qui devient concave vers le haut. La différence entre la courbe de *Paw* en conditions passives et lors d'un effort inspiratoire du patient représente donc la pression générée par les muscles respiratoires du patient (*Pmus*), et l'aire comprise entre ces deux courbes représente le *PTPes* (39) (Fig. 3).

Ainsi, à débit d'insufflation constant, plus le patient fait un effort inspiratoire important, moins la pression d'assistance délivrée dans les voies aériennes est importante, faisant de la VAC un mode peu adapté à la ventilation assistée. Il est cependant possible d'augmenter l'assistance à volume courant de consigne constant en augmentant le débit d'insufflation (34, 40). Cette modification se fait néanmoins au prix d'une diminution du temps d'insufflation.

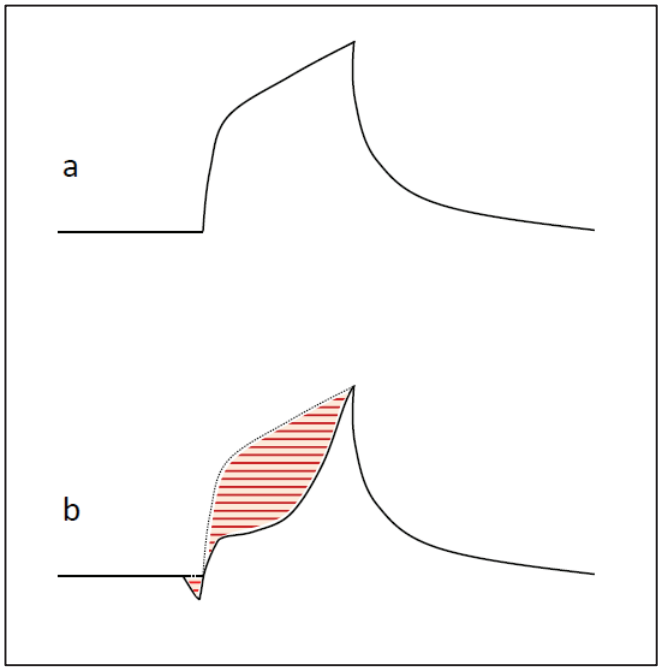

Figure 3 Pression des voies aériennes à débit d'insufflation constant en conditions passives (a) et au cours d'un effort inspiratoire (b). L'aire entre les courbes a et b (zonne achurée), liée à l'effort inspiratoire du patient, représente a valeur du *PTPes*.

Or, l'association d'un débit d'insufflation relativement élevé et d'un volume courant dit « protecteur » (41) (6 ml/kg de poids idéal théorique) peut conduire à un temps d'insufflation plus court que le temps inspiratoire neural du patient, générant des asynchronies fréquemment observées en VAC : le cycle court et le double déclenchement (22, 42) (Fig. 1). Au cours d'un double déclenchement, l'effort inspiratoire du patient se prolonge suffisamment au-delà de la fin de l'insufflation pour déclencher immédiatement un deuxième cycle. Ainsi, au cours d'un seul effort respiratoire, le patient reçoit le double du volume courant préréglé par le clinicien

et les objectifs d'une ventilation protectrice ne sont plus satisfaits. Parmi les réponses possibles à apporter en cas de double déclenchement (diminuer le débit d'insufflation, augmenter le temps de pause télé-inspiratoire, augmenter la sédation du patient, passer en ventilation spontanée avec aide inspiratoire), si le patient est en phase de sevrage de la ventilation mécanique, le passage en ventilation spontanée avec aide inspiratoire est la meilleure option (42).

1.2.2. Interactions patient-ventilateur au cours de la ventilation spontanée avec aide inspiratoire

La ventilation spontanée avec aide inspiratoire (VSAI) est le mode de ventilation assistée le plus utilisé actuellement (20). En VSAI, tous les cycles du ventilateur sont déclenchés par le patient (6) lorsque le trigger inspiratoire (généralement en débit) est atteint. Au cours de l'insufflation, la consigne donnée au ventilateur est de maintenir une pression constante (la pression d'aide inspiratoire) au-dessus de la PEP. Le ventilateur adapte donc son débit tout au long de l'insufflation afin de maintenir la pression d'aide inspiratoire à sa valeur réglée. Le débit est ainsi maximal en début d'insufflation puis prend un aspect décélérant. La consigne de cyclage qui met fin à l'insufflation est une valeur relative du débit d'insufflation maximal. Par défaut sur les ventilateurs cette valeur est réglée à 25%. Ainsi, lorsque le débit d'insufflation atteint 25% de sa valeur maximale, l'insufflation prend fin et l'expiration est autorisée. Les interactions patient-ventilateur sont donc relativement complexes en VSAI. En effet lorsque la pression d'aide inspiratoire est augmentée, l'effort inspiratoire du patient diminue (2, 6, 43-45), mais dans le même temps le temps d'insufflation et le volume courant augmentent (2, 43-46). Par ailleurs, à niveau d'aide inspiratoire identique, lorsque le patient fait un effort inspiratoire plus important, le débit d'insufflation augmente afin de maintenir la pression d'assistance fixe, et ainsi le temps d'insufflation et le volume courant augmentent

eux aussi (Fig. 4). Enfin, à effort inspiratoire et pression d'assistance fixes, le débit d'insufflation maximal ainsi que sa pente de décroissance dépendent aussi de la mécanique respiratoire du patient (47-50). Par exemple, la pente est d'autant plus raide que la compliance est faible, influençant alors la valeur du temps d'insufflation et celle du volume courant (50).

Les valeurs du temps d'insufflation et du volume courant en VSAI dépendent donc du niveau d'aide inspiratoire réglé, de l'effort inspiratoire du patient et de sa mécanique respiratoire, l'effort inspiratoire étant lui-même influencé par le niveau d'aide inspiratoire.

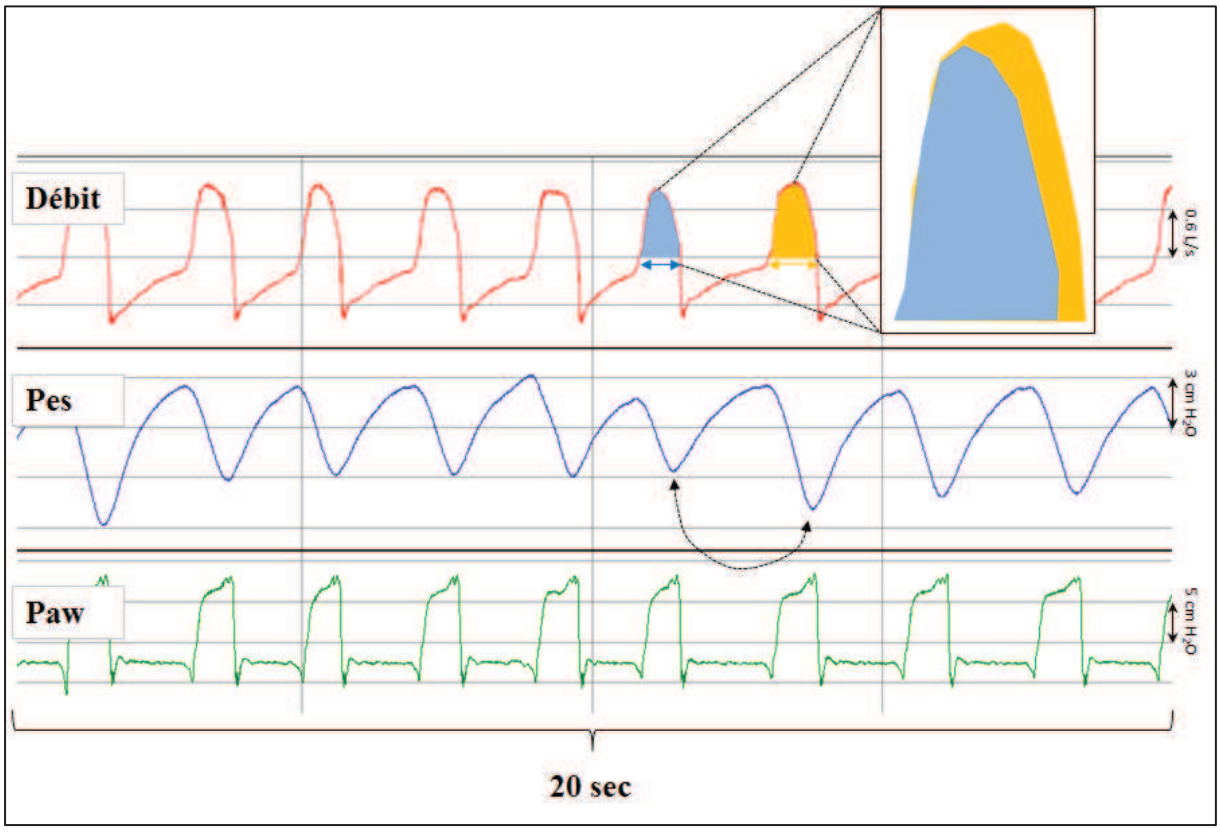

Figure 4 Effets d'une modification de l'effort inspiratoire en VSAI. Les courbes représentent (de haut en bas) : le débit des voies aériennes, la pression œsophagienne (*Pes*), et la pression des voies aériennes (*Paw*). La double flèche en pointillés pointe deux efforts inspiratoires différents (plus la dépression œsophagienne est importante plus l'effort inspiratoire est important). L'encadré représente un grossissement et une superposition des deux aires sous la courbe du débit d'insufflation (soit des deux volumes courants) aux deux efforts différents. Lorsque l'effort inspiratoire augmente, on observe une augmentation du débit d'insufflation maximal, du volume courant et du temps d'insufflation.

Ces différents effets permettent d'expliquer la possible survenue d'altérations majeures des interactions patient-ventilateur en VSAI. En effet, lorsque le clinicien augmente l'aide inspiratoire, le temps d'insufflation du ventilateur augmentant il peut largement dépasser le temps inspiratoire propre (ou neural) du patient (5, 46, 51-55). Ce phénomène a pour effet une diminution relative du temps expiratoire (56). Comme dans le même temps le volume courant insufflé est plus important (2, 43-46), l'augmentation de l'aide inspiratoire en VSAI peut rapidement conduire à la survenue d'une hyperinflation dynamique (5, 51, 52), qui correspond à une expiration incomplète. Ce phénomène survient naturellement d'autant plus fréquemment que le patient présente une constante de temps (*Rrs* x *Crs*) élevée (52, 57). Lors d'un tel phénomène, il persiste donc un volume télé-expiratoire au-dessus de la capacité résiduelle fonctionnelle, générant une *PEP* intrinsèque (58, 59). En début d'inspiration, le patient doit donc développer une pression musculaire supérieure à la *PEP* intrinsèque afin de déclencher le ventilateur (5, 51, 58, 59). A l'extrême, son effort demeure insuffisant et aucun cycle n'est délivré par le ventilateur, il s'agit alors de l'asynchronie la plus fréquente en VSAI : l'effort inefficace (1, 3, 5, 22, 46, 51-55, 57, 60-62) (Fig. 5).

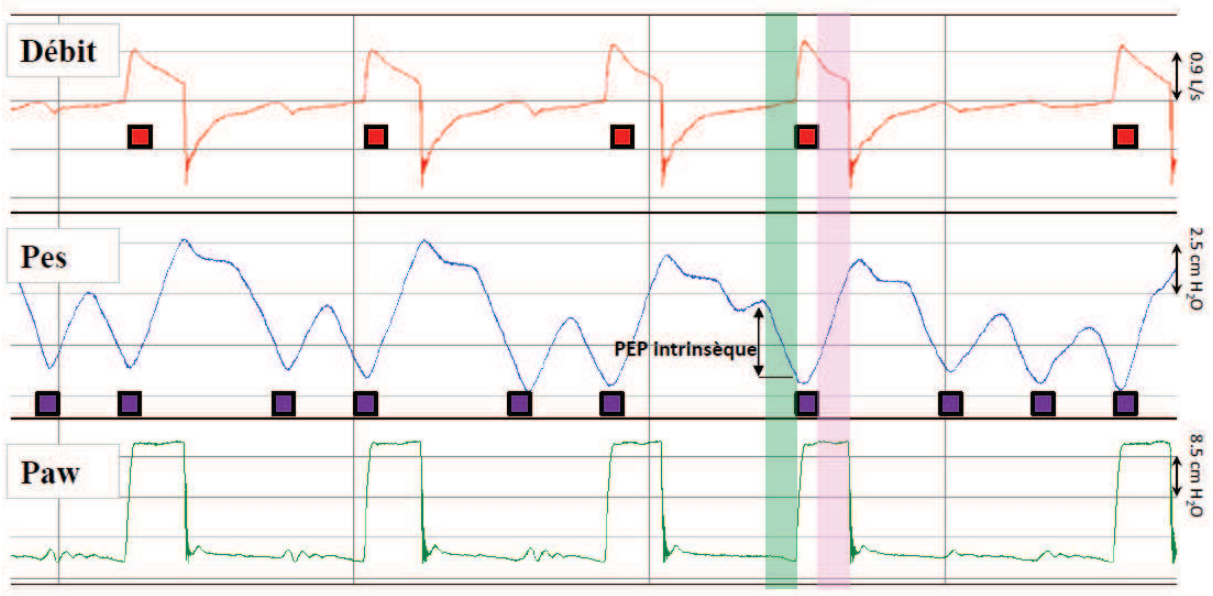

Figure 5 Efforts inefficaces au cours de la VSAI. Les courbes représentent (de haut en bas) : le débit dans les voies aériennes, la pression œsophagienne (*Pes*), et la pression dans les voies aériennes (*Paw*). Les carrés rouges pointent les cycles délivrés par le ventilateur alors que les carrés bleus pointent les efforts inspiratoires du patient. On observe que de nombreux efforts inspiratoires ne sont pas récompensés, il s'agit d'efforts inefficaces. La majeure partie de l'effort inspiratoire du patient est réalisée pour dépasser le niveau de *PEP* intrinsèque (surlignage vert) et déclencher le ventilateur. Par ailleurs, l'insufflation se poursuit bien au-delà du temps inspiratoire neural du patient (surlignage rose), expliquant pour partie la genèse du phénomène d'hyperinflation dynamique à l'origine des efforts inefficaces. Le patient représenté ci-dessus est le même que celui représenté Fig. 3. Cependant, à la Fig.3 l'aide inspiratoire était de 10 cm H_2O alors que ci-dessus elle est de 25 cm H_2O.

Si la survenue d'efforts inefficaces représente un signe de sur-assistance en VSAI devant inciter le clinicien à diminuer le niveau d'aide inspiratoire (21), déterminer le niveau d'aide inspiratoire optimale pour un patient donné à un instant donné demeure néanmoins complexe en pratique clinique. En effet, on ne dispose pas de mesure objective en routine de l'effort respiratoire du patient mais uniquement de signaux indirects (signes cliniques de détresse respiratoire attestant d'une sous-assistance, survenue d'efforts inefficaces témoignant d'une sur-assistance). Par ailleurs, la modification de l'aide inspiratoire modifiant à la fois l'effort inspiratoire du patient, le temps d'insufflation et le volume courant, il est difficile de trouver

le niveau d'aide inspiratoire qui corresponde au meilleur compromis entre ces différents intervenants des interactions patient-ventilateur (Fig. 6).

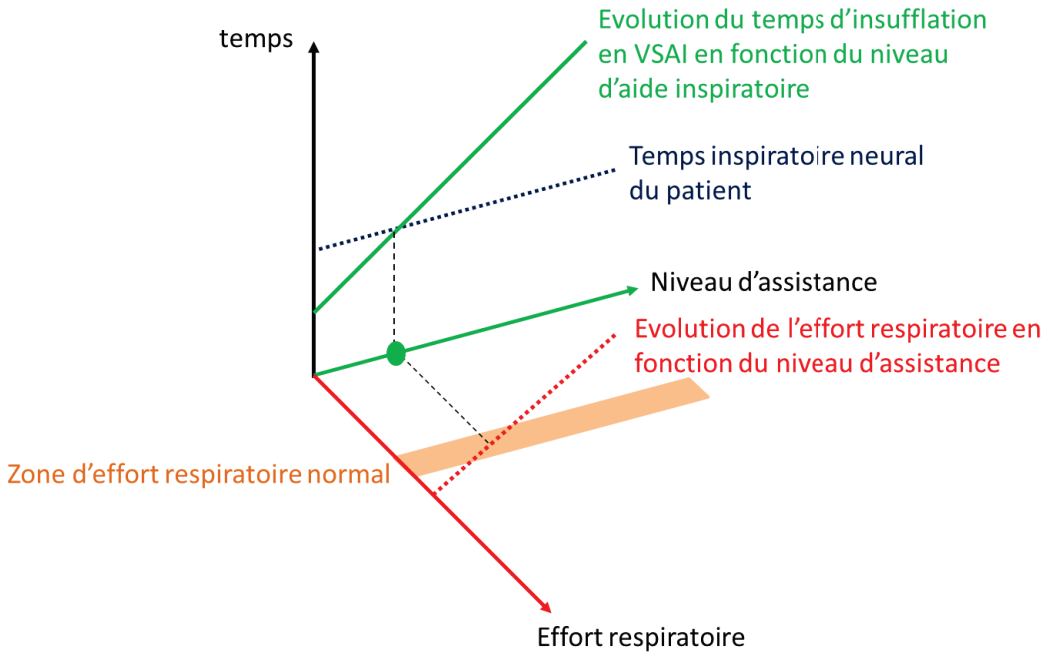

Figure 6 Représentation simultanée de certains intervenants des interactions patient-ventilateur en fonction du niveau d'assistance en VSAI. Lorsque l'aide inspiratoire augmente, l'effort inspiratoire du patient diminue, mais dans le même temps le temps d'insufflation augmente, dépassant le temps inspiratoire neural du patient. Cette figure représente un niveau d'aide inspiratoire théoriquement idéal, c'est-à-dire permettant une synchronisation temporelle parfaite entre l'assistance du ventilateur et l'inspiration du patient ainsi qu'un effort inspiratoire normal. Il est possible que chez certains patients, un tel niveau d'assistance n'existe pas, par exemple parce que le niveau d'assistance entrainant un effort normal s'accompagne d'un temps d'insufflation prolongé. Par ailleurs, d'autres paramètres sont modifiés par la modification de l'aide inspiratoire comme le volume courant. Quoi qu'il en soit, si un tel niveau existe, il reste très difficile à déterminer en pratique clinique faute de monitorage en routine de l'effort inspiratoire du patient.

1.2.3. Synthèse sur les modes classiques

Au cours des modes classiques de ventilation assistée, la modification de l'assistance du respirateur modifie non seulement la quantité d'effort inspiratoire du patient mais aussi sa synchronisation temporelle avec l'insufflation du ventilateur ainsi que, souvent, le volume

délivré. Les asynchronies patient-ventilateurs sont fréquemment observées puisqu'elles surviennent avec une incidence élevée chez un quart des patients (22, 61). La survenue fréquente de ces asynchronies est associée à une prolongation de la ventilation mécanique (22, 61, 63), pointant l'importance des interactions patient-ventilateur en ventilation assistée.

Du fait des modalités de fonctionnement propres aux modes classiques de ventilation assistée, il demeure donc complexe en routine d'optimiser les interactions patient-ventilateur tant en termes de synchronisation qu'en termes d'adaptation aux besoins ventilatoires et à l'effort respiratoire du patient. Faute de monitorage de l'effort respiratoire du patient, le niveau d'assistance qui permet le meilleur compromis entre ces différents intervenants des interactions patient-ventilateur est difficile à déterminer en pratique clinique.

1.3. Nouveaux algorithmes de ventilation et interactions patient-ventilateur en ventilation invasive : les modes assistés proportionnels

1.3.1. Généralités sur les modes proportionnels

Le principe général des modes de ventilation proportionnelle est de délivrer une assistance directement en proportion de l'effort respiratoire du patient tout au long de l'insufflation (64) (Fig. 7). Ainsi, la *Paw* est directement proportionnelle à un signal d'effort respiratoire, et c'est le type de signal utilisé par le ventilateur qui différencie les deux principaux modes d'assistance proportionnelle actuellement disponibles en clinique : estimation des pressions résistive et élastique à partir de mesures de la mécanique respiratoire et des signaux de débit et de volume instantanés générant une assistance proportionnelle à la pression musculaire pour la PAV+ (propotional assist ventilation with load-adjustable gain factors, voir paragraphe 1.3.2.1) (65-67), signal d'activité électrique du diaphragme pour la NAVA (neurally adjusted ventilatory assist, voir paragraphe 1.3.3.1) (68).

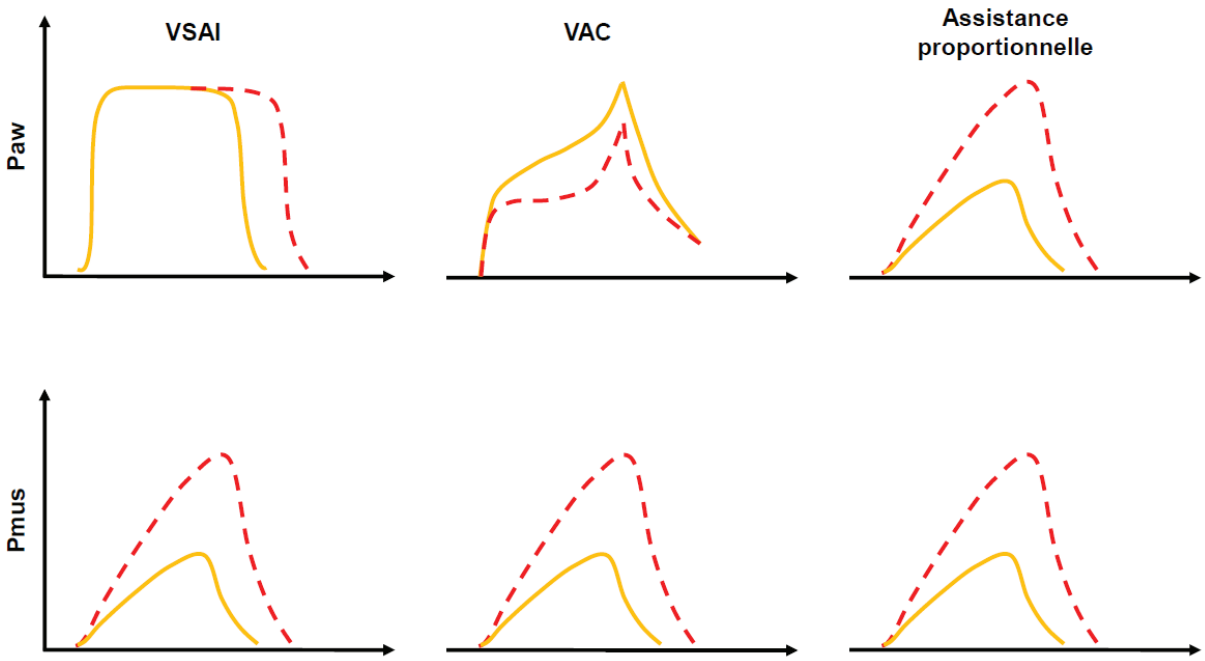

Figure 7 Représentation schématique de l'évolution de la pression d'assistance (pression dans les voies aériennes, *Paw*) lors d'une augmentation de l'effort respiratoire (pression musculaire, *Pmus*) en VSAI, VAC et au cours des modes d'assistance proportionnelle. Lorsque l'effort respiratoire du patient augmente, la *Paw* reste identique (aide inspiratoire + *PEP*) au cours de la VSAI puisque c'est la consigne donnée au respirateur (voir paragraphe 1.2.2), elle diminue en VAC car la consigne est de maintenir un débit d'insufflation et un temps d'insufflation constants (voir paragraphe 1.2.1), en revanche elle augmente car elle reste proportionnelle à l'effort respiratoire du patient tout au long de l'insufflation au cours des modes d'assistance proportionnelle.

1.3.2. La PAV+

1.3.2.1. Principes de fonctionnement de la PAV+

Historiquement, la ventilation assistée proportionnelle (PAV pour proportional assist ventilation) a été décrite peu de temps après l'introduction de la VSAI (65, 69). Cependant elle nécessitait pour fonctionner des mesures manuelles répétées de la mécanique respiratoire, ce qui constituait un obstacle majeur à son utilisation clinique. Plus récemment, de nouveaux algorithmes ont permis d'automatiser les mesure de mécanique respiratoire avec une adaptation en continue (66, 67), rendant le mode fonctionnel pour une utilisation clinique sous l'appellation PAV+, disponible sur le ventilateur PB840 (Covidien, Galway, Ireland). Dans

un but de simplification nous nous limiterons à la description du mode de fonctionnement de la PAV+.

Ce mode utilise l'équation de mouvement du système respiratoire pour fonctionner. Au cours de la ventilation assistée, cette équation s'écrit ainsi (38):

$$\Delta P_{tot(t)} = \Delta P_{aw(t)} + \Delta P_{mus(t)} = R \times V'_{(t)} + \frac{V_{(t)}}{Crs} \qquad [Equation\ 1]$$

Où ΔP_{tot} est la pression motrice totale, c'est-à-dire l'addition de la pression musculaire générée par les muscles inspiratoires du patient (ΔP_{mus}) et de la pression des voies aériennes générée par le ventilateur (ΔP_{aw}) ; R représente les résistances du système respiratoire, V' le débit dans les voies aériennes, V le volume insufflé et Crs la compliance du système respiratoire.

Au cours du mode PAV+, les résistances et la compliance du système respiratoire sont automatiquement mesurées par le respirateur au moyen de micro-occlusions télé-inspiratoires de 300 ms (66, 67), réalisées tous les quatre à dix cycles de manière randomisée et moyennées au moyen d'une moyenne mouvante avec élimination des valeurs aberrantes (Fig. 8). Ainsi le ventilateur dispose d'une mise à jour permanente des valeurs de résistance et de compliance du système respiratoire. Le ventilateur mesurant par ailleurs les débits et volumes instantanés, il est capable de calculer à chaque instant la valeur de la pression totale. En PAV+, l'assistance délivrée par le ventilateur, c'est-à-dire la ΔP_{aw}, est réajustée de manière instantanée pour rester un pourcentage de la pression totale, ce pourcentage étant le gain réglé par le clinicien. En d'autres termes, le clinicien ajuste le pourcentage de la pression totale prise en charge par le respirateur, le reste étant assumé par le patient. Ainsi :

$$\Delta P_{aw(t)} = Gain \times \Delta P_{tot(t)} \qquad [Equation\ 2]$$

En combinant simplement les *Equations 1 et 2*, on obtient la relation qui existe entre $\Delta P_{aw(t)}$ et $\Delta P_{mus(t)}$ en PAV+, qui correspond au sens physiologique réel de la PAV+, qui est finalement de délivrer une assistance directement proportionnelle à la pression musculaire du patient (Fig. 7):

$$\Delta P_{aw(t)} = \Delta P_{mus(t)} \times \frac{Gain}{1-Gain} \qquad [Equation\ 3]$$

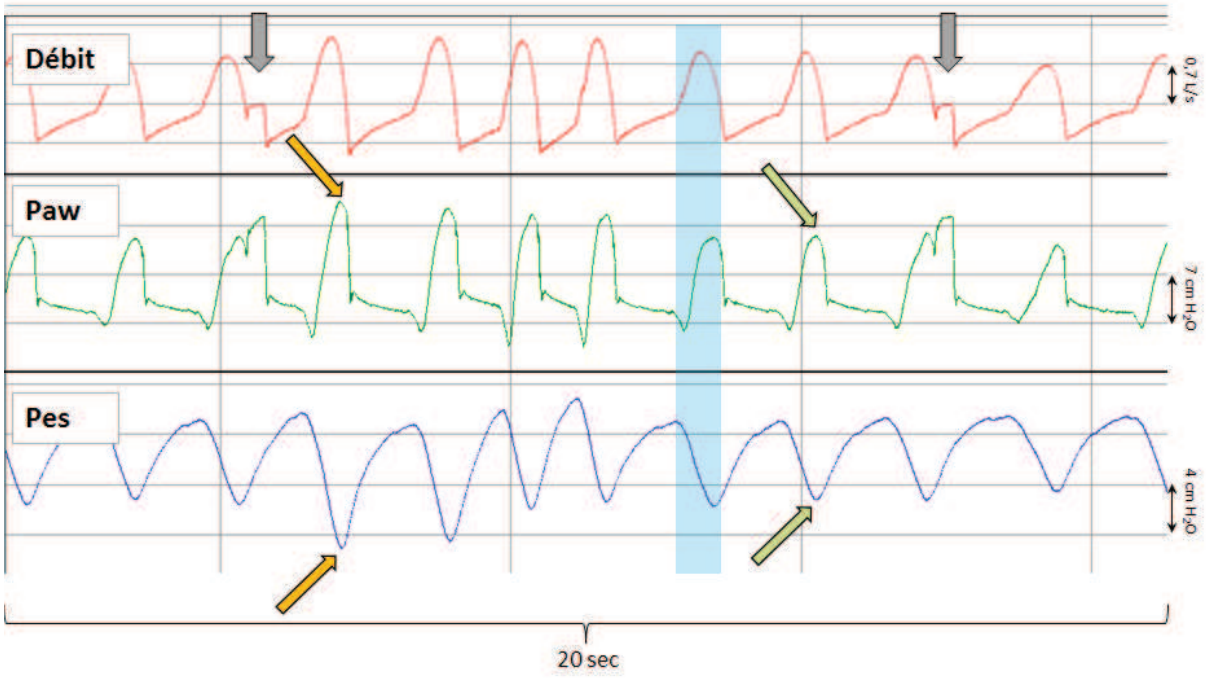

Figure 8 Enregistrement d'un patient en mode PAV+. Les courbes représentent (de haut en bas) : le débit dans les voies aériennes, la pression dans les voies aériennes (*Paw*), et la pression œsophagienne (*Pes*). Les micro-occlusions télé-inspiratoires (flèches grises) sont réalisées de manière automatique et permettent une mise à jour permanente des mesures de mécanique respiratoire. La *Paw* est proportionnelle tout au long du cycle respiratoire à la pression musculaire du patient. Ainsi, un effort plus important (flèches orange) est plus assisté qu'un effort moins important (flèche vertes). Par ailleurs, le temps d'insufflation est superposé au temps inspiratoire neural du patient (surlignage bleu).

1.3.2.2. Interactions patient-ventilateur en PAV+

En PAV+, l'assistance étant proportionnelle à la pression musculaire du patient, la variabilité naturelle cycle à cycle du système respiratoire est respectée (70). Par ailleurs, la consigne de cyclage est excellente. En effet, lorsqu'il n'y a plus de pression musculaire, il n'y a plus d'assistance, et ce quel que soit le niveau de gain réglé. Le temps d'insufflation reste donc très proche du temps inspiratoire neural du patient (46, 71).

Lorsque le clinicien augmente le niveau d'assistance, l'effort respiratoire du patient diminue, et ainsi le volume courant résultant varie peut (46). La relative stabilité du volume courant, le respect de sa variabilité cycle à cycle et la qualité du cyclage limitent grandement la genèse d'une hyperinflation dynamique, et donc la survenue d'efforts inefficaces (46, 71, 72). De plus, à niveau d'assistance stable, la PAV+ s'adapte mieux que la VSAI aux modifications de la charge respiratoire (73, 74), c'est à dire à l'augmentation des résistances ou à une diminution de la compliance du système respiratoire. Le confort est aussi meilleur (75). En comparaison à la VSAI, les interactions patient-ventilateur sont donc largement améliorées en PAV+. Les expériences cliniques rapportées sont cependant rares (72), et la question du réglage du gain reste ouverte.

1.3.3. La NAVA

1.3.3.1. Principes de fonctionnement de la NAVA

La NAVA, décrite pour la première fois par Sinderby en 1999 (68), est une ventilation assistée neuro-asservie, c'est-à-dire qu'elle délivre une assistance en pression directement proportionnelle à l'activité électrique du diaphragme (*EAdi*, en µvolt). Le rapport de proportionnalité, appelé niveau de NAVA (en cm H_2O.µvolt^{-1}) est réglé par le clinicien. Ainsi, en NAVA :

$$Paw = EAdi \times Niveau\ de\ NAVA$$

Le recueil de l'*EAdi* se fait au moyen d'un cathéter œsophagien muni d'électrodes positionnées en regard du diaphragme crural (Fig. 9) (76). Ce cathéter dispose d'une connectique permettant de le relier au module NAVA disponible sur le ventilateur Servo-i (Maquet Critical Care, Solna, Suède). Chaque électrode recueille un signal électrique composé de l'électromyogramme (EMG) du diaphragme crural mais aussi de signaux parasites dont le signal ECG. Les signaux des différentes électrodes sont traités afin d'aboutir à l'*EAdi*. Schématiquement : les signaux sont sommés à l'aide d'algorithmes de correction du mouvement du diaphragme par rapport à la position des électrodes, les signaux parasites dont le signal ECG sont filtrés, Le signal EMG ainsi obtenu est rendu positif au moyen d'une moyenne quadratique, et l'enveloppe de ce signal constitue l'*EAdi*. S'agissant d'un signal neural, la durée de l'*EAdi* correspond fidèlement au temps inspiratoire du patient (77). Par ailleurs, son intensité est proportionnelle à celle de la *Pdi* (43). L'insufflation prend fin en NAVA lorsque l'*EAdi* atteint 70% de sa valeur maximale (Fig. 10).

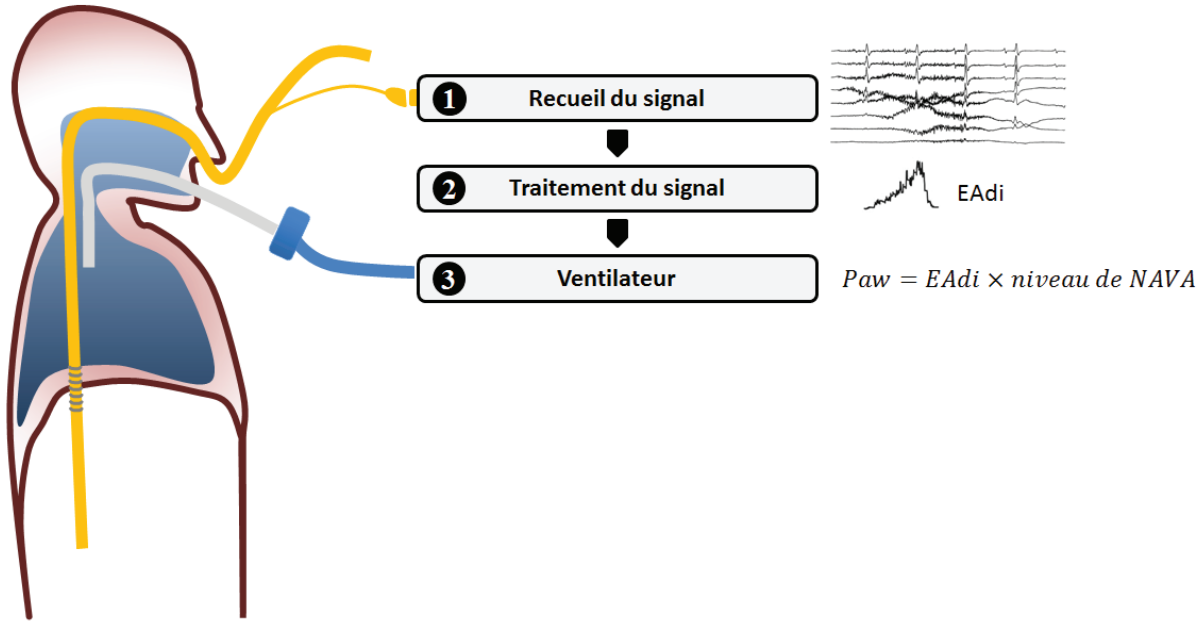

Figure 9 Principes de fonctionnement de la NAVA. Un cathéter œsophagien muni d'électrodes en regard du diaphragme crural permet le recueil du signal d'activité électrique du diaphragme (*EAdi*). Le ventilateur délivre une *Paw* = *EAdi* x niveau de NAVA, ce dernier étant réglé par le clinicien.

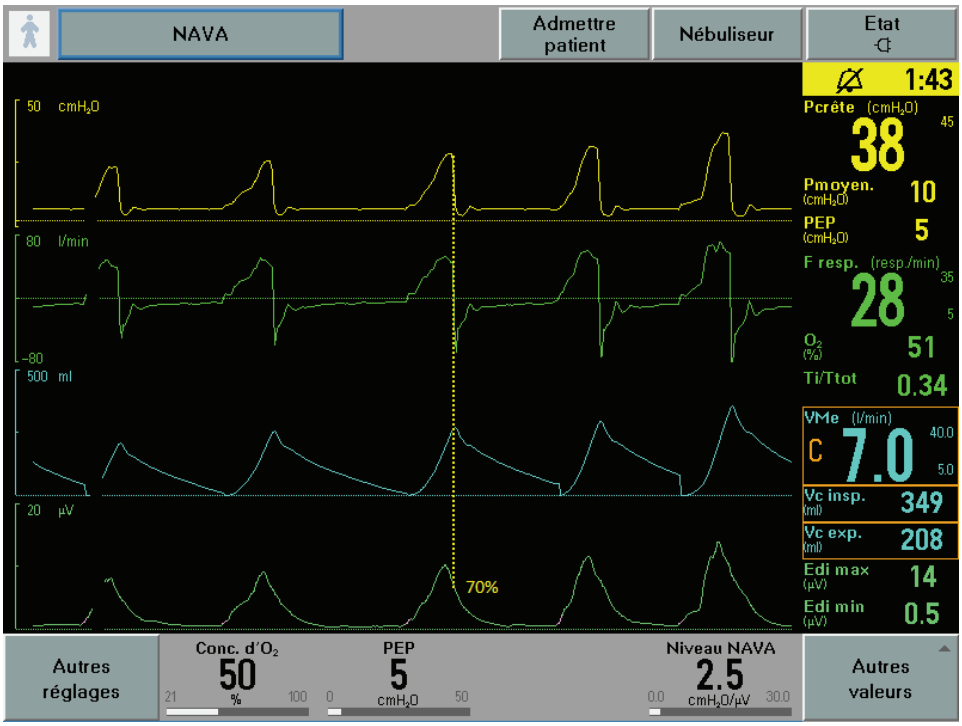

Figure 10 Capture d'écran d'un patient en mode NAVA. Au cours de l'insufflation, la *Paw* est à chaque instant égale à la valeur de *l'EAdi* (en µvolt) multipliée par le niveau de NAVA (en cm H_2O.µvolt^{-1}). Le cyclage intervient lorsque *l'EAdi* atteint 70% de la valeur de son pic (pointillés jaunes).

1.3.3.2. Interactions patient-ventilateur en NAVA

En NAVA, l'assistance est proportionnelle au signal neural d'activation du diaphragme. Ainsi, l'insufflation du ventilateur se superpose dans le temps à la contraction diaphragmatique (54, 78), et ce quelques soit les conditions de mécanique respiratoire et en particulier la valeur de la *PEP* intrinsèque. Par ailleurs, la variabilité naturelle cycle à cycle du système respiratoire et sa complexité sont respectées (53, 70, 79).

Dans les études expérimentales et cliniques, lorsque le niveau de NAVA est augmenté, l'*EAdi* diminue, et ainsi le volume courant résultant ne varie que peu, indiquant qu'il s'agit du volume « ciblé » par le patient (53, 54, 80-83). De la même manière qu'en PAV+, la relative stabilité du volume courant, le respect de sa variabilité cycle à cycle et la qualité du cyclage limitent grandement la possibilité d'une hyperinflation dynamique « iatrogène ». La proportionnalité de la *Paw* directement sur le signal neural ainsi que la limitation de l'hyperinflation dynamique empêchent la survenue d'efforts inefficaces en NAVA (53, 55, 78, 84). Des double-déclenchements sont cependant rapportés, généralement à une incidence faible, du fait d'accidents sur le signal *EAdi* atteignant la consigne de cyclage en cours d'inspiration (78). En comparaison à la VSAI, la NAVA améliore constamment les interactions patient-ventilateur (53-55, 70, 78, 81, 85-88). Cependant, si la valeur de l'*EAdi* est proportionnelle à l'effort inspiratoire du patient (43, 80, 89), ce rapport de proportionnalité est différent d'un patient à l'autre (89), il a été peu étudié à des niveaux de NAVA différents et de manière longitudinale dans le temps, et il dépend probablement de la contribution relative – bien que faible en NAVA (90) – des muscles respiratoires accessoires. Ajuster le niveau de NAVA en pratique clinique demeure donc un sujet de recherche.

1.3.4. Synthèse sur les modes proportionnels

C'est le caractère proportionnel (incluant une consigne de cyclage performante) de l'assistance bien plus que le signal sur lequel elle est asservie qui explique la majorité des interactions patient-ventilateur au cours des modes proportionnels, et en particulier la diminution des asynchronies patient-ventilateur. Ainsi, Terzi et coll. retrouvaient une diminution des asynchronies patient-ventilateur lors de l'augmentation de l'assistance en NAVA en comparaison à la VSAI, que le déclenchement du cycle se fasse avec un trigger neural ou au moyen d'un trigger classique en débit (55). Plus récemment, Schmidt et coll. ont rapporté des interactions patient-ventilateur comparables entre la PAV+ et la NAVA en ce qui concerne le pattern respiratoire, sa variabilité, la diminution de la survenue d'efforts inefficaces en comparaison à la VSAI (70). Les différences notables entre la PAV+ et NAVA concernent en revanche les signaux sur lesquels ces deux modes sont asservis : meilleure adaptation aux variations de la charge respiratoire pour la PAV+ (73, 74) mais décalage au déclenchement du cycle inhérent aux triggers en débit (91) et rapport de proportionnalité moins fiable en cas de *PEP* intrinsèque ; synchronisation sur l'activité électrique du patient pour la NAVA avec déclenchement immédiat du cycle (91) mais proportionnalité de l'assistance variable d'un patient à l'autre pour un même niveau de NAVA (89), contraintes techniques supplémentaires (positionnement du cathéter *EAdi*, stabilité du signal dans le temps) (76) et asynchronies propres au mode (78). Quoi qu'il en soit la modification du niveau d'assistance au cours des modes proportionnels modifiant essentiellement l'effort respiratoire du patient et peu ou pas la synchronisation patient-ventilateur et le pattern respiratoire (en particulier le volume courant), il semblerait optimal au regard des interactions patient-ventilateur d'ajuster le niveau d'assistance en fonction du niveau d'effort respiratoire réalisé par le patient (Fig. 11).

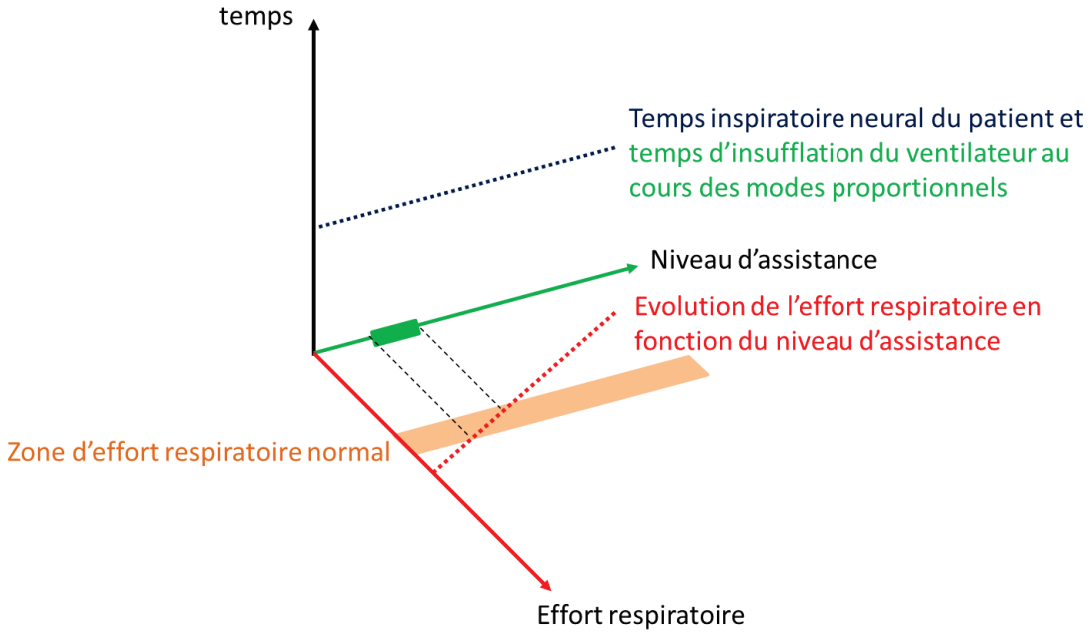

Figure 11 Interactions patient-ventilateur au cours des modes proportionnels. Les modes proportionnels sont caractérisés par un temps d'insufflation très proche du temps inspiratoire neural du patient quelque soit le niveau d'assistance. Par ailleurs, si le volume courant était représenté, celui-ci varierait peu en fonction du niveau d'assistance. En revanche, l'effort respiratoire diminue avec l'augmentation du niveau d'assistance, c'est le principe de la ventilation assistée. Au cours des modes proportionnels, définir une zone d'effort respiratoire normale ou acceptable comme cible thérapeutique lors de l'ajustement du niveau d'assistance correspond donc en théorie à la meilleure manière d'optimiser les interactions patient-ventilateur en ventilation assistée.

1.4. Interactions patient-ventilateur en ventilation non-invasive

Actuellement la ventilation non-invasive (VNI) est très majoritairement réalisée en VSAI (92). Comme décrit précédemment (voir chap. 1.2.2), ce mode utilise le signal de débit des voies aériennes pour déclencher (trigger inspiratoire) et finir (consigne de cyclage) le cycle, c'est à dire synchroniser l'assistance ventilatoire aux efforts inspiratoires du patients. Le principal problème en VNI au regard des interactions patient-ventilateur concerne la présence de fuites autour de l'interface, quasiment inévitables en pratique clinique (93). En effet, le débit de fuites est à même de considérablement perturber le signal de débit des voies aériennes et donc la synchronisation patient-ventilateur. Ainsi, une fuite expiratoire peut mimer un appel inspiratoire du patient et déclencher un cycle en dehors de tout effort inspiratoire, il s'agit d'un auto-déclenchement (94) (Fig. 1 et 12). Lors de la survenue de fuites au cours de l'insufflation, le débit délivré par le ventilateur est maintenu à un niveau élevé afin de maintenir la pressurisation malgré les fuites et n'atteint pas ou que très tardivement la consigne de cyclage, générant une insufflation prolongée (95) (Fig. 1 et 12). Lors de l'utilisation de ventilateurs de réanimation, initialement conçus pour fonctionner en l'absence de fuite, les asynchronies patient-ventilateur ont donc été rapportées avec une fréquence particulièrement élevée puisqu'au qu'au moins 10% des cycles étaient asynchrones chez environ 40% des patients étudiés (24).

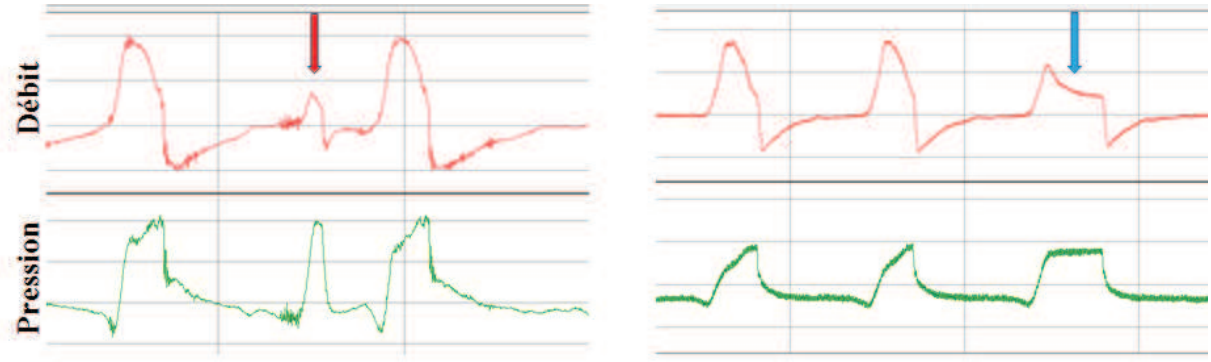

Figure 12 Asynchronies liées aux fuites en ventilation non-invasive. L'enregistrement de gauche rapporte un auto-déclenchement (flèche rouge), qui se manifeste généralement sous la forme d'un cycle bref d'allure tronquée au cours de l'expiration. A droite est représentéé une insufflation prolongée (flèche bleue).

1.5. Nouveaux algorithmes de ventilation et interactions patient-ventilateur en ventilation non-invasive : les algorithmes VNI et les ventilateurs dédiés

Du fait de la propension du débit de fuite – variable selon le patient, l'interface (93), les réglages du ventilateur (95), au cours du temps – à perturber le signal de débit des voies aériennes et ainsi l'efficacité et la synchronisation de la pressurisation en VNI, les constructeurs ont développé ces dernières années des algorithmes supposés optimiser le fonctionnement des ventilateurs de réanimation en présence de fuite. Ces algorithmes VNI, communément appelés « modes VNI », sont censés par exemple estimer la fuite, la compenser, personnaliser la sensibilité des triggers en fonction de son niveau. Ils sont cependant différents d'un ventilateur à l'autre et souvent couverts par le secret industriel. En marge de ces ventilateurs classiques de réanimation, des ventilateurs spécifiquement dédiés à la conduite de la VNI ont par ailleurs été développés. Il s'agit de ventilateurs à turbine fonctionnant généralement avec un circuit monobranche et une fuite intentionnelle. Ils sont issus des technologies des ventilateurs de domicile dont les algorithmes ont été depuis longtemps développés dans le but d'optimiser le confort et la synchronisation patient-ventilateur en présence de fuites. Les quelques données disponibles sur banc d'essai évaluant

les performances en termes de pressurisation et de synchronisation patient-ventilateur de certains de ces algorithmes VNI et ventilateurs dédiés suggèrent une certaine efficacité (96-98). Cependant, le choix du ventilateur pour réaliser la VNI en aigu demeure davantage le reflet d'habitudes locales (99, 100) que d'une approche basée sur des preuves faute de données suffisantes disponibles, en particulier cliniques.

2. PRINCIPAUX OBJECTIFS DE LA THESE

L'objectif de ce travail de thèse était d'évaluer l'intérêt potentiel des nouveaux algorithmes de ventilation dans l'optimisation des interactions patient-ventilateur:

1. ***Intérêt des nouveaux algorithmes de ventilation dans l'optimisation des interactions patient-ventilateur en ventilation invasive :*** évaluer la possibilité de personnaliser l'assistance du ventilateur en fonction de l'effort respiratoire du patient lors de l'utilisation des modes proportionnels.

2. ***Intérêt des nouveaux algorithmes de ventilation dans l'optimisation des interactions patient-ventilateur en ventilation non-invasive :*** Evaluer si les algorithmes VNI implémentés sur les ventilateurs de réanimation et les ventilateurs dédiés à la VNI améliorent la synchronisation patient-ventilateur en VNI.

3. DEMARCHE SCIENTIFIQUE ET CONDUITE DE LA THESE

La thèse repose sur quatre études (voir chap. 5).

Intérêt des nouveaux algorithmes de ventilation dans l'optimisation des interactions patient-ventilateur en ventilation invasive :

Etude 1 : *Evaluation clinique de la faisabilité d'ajuster le gain en PAV+ avec pour but de maintenir l'effort respiratoire du patient dans une zone normale.* Ce travail a montré qu'il était possible d'ajuster le gain en PAV+ en ciblant un effort respiratoire normal. De tels réglages étaient par ailleurs simples à réaliser et la plupart du temps suffisants pour ventiler les patient depuis le début de la phase de sevrage de la ventilation mécanique jusqu'à l'extubation.

Etude 2 : *Comparaison d'une titration de l'assistance en NAVA et en VSAI basée sur l'analyse des indices d'effort respiratoire.* Cette étude pointait le fait que la relation entre l'EAdi et l'effort inspiratoire est non seulement variable d'un patient à l'autre, mais aussi selon le niveau de NAVA, rendant difficile d'envisager ajuster ce dernier en ciblant directement une valeur d'effort inspiratoire du patient. Cette étude a néanmoins permis de préciser les bornes d'utilisation de la NAVA et de corréler des niveaux d'aide inspiratoire – avec lesquels les cliniciens sont familiers – à des niveaux de NAVA en termes d'effort respiratoire.

Intérêt des nouveaux algorithmes de ventilation dans l'optimisation des interactions patient-ventilateur en ventilation non-invasive :

Etude 3 : *Evaluation clinique de l'incidence des asynchronies patient-ventilateur en VNI avec et sans l'utilisation de l'algorithme VNI sur des ventilateurs variés de réanimation.* Ce travail rapportait une diminution de l'incidence des asynchronies liées aux fuites lors de l'activation de l'algorithme VNI sans diminuer significativement l'incidence globale des asynchronies patient-ventilateur.

Etude 4 : *Evaluation clinique et sur banc d'essai de la synchronisation patient-ventilateur en VNI avec l'utilisation de ventilateurs de réanimation avec ou sans activation de l'algorithme VNI et de ventilateurs dédiés à la VNI.* L'étude clinique chez des patients de réanimation et l'étude sur banc d'essai se validaient mutuellement du fait de résultats très concordants. Ceux-ci pointaient l'hétérogénéité des algorithmes VNI sur les ventilateurs de réanimation et retrouvaient une meilleure synchronisation patient-ventilateur avec l'utilisation de ventilateurs dédiés à la VNI pour des qualités de pressurisation par ailleurs identiques.

4. METHODES

4.1. Mesure au lit du malade du pic de pression musculaire en mode PAV+, et choix d'un intervalle de pic de pression musculaire comme cible thérapeutique

La PAV+ est un mode de ventilation proportionnelle qui délivre une assistance en proportion de la pression musculaire du patient (65) (voir chapitre 1.3.2.1) :

$$\Delta P_{aw(t)} = \Delta P_{mus(t)} \times \frac{Gain}{1-Gain} \qquad [Equation\ 3]$$

A partir de l'*Equation 3* il devient possible en mode PAV+ de recalculer au lit du malade le pic de pression musculaire à chaque effort inspiratoire de la manière suivante :

$$P_{mus,Peak} = (P_{aw,Peak} - PEP) \times \frac{1-Gain}{Gain} \qquad [Equation\ 4]$$

Au cours de la PAV+, l'assistance respiratoire pourrait donc être ajustée avec le but de maintenir le pic de pression musculaire ($P_{mus,Peak}$) dans un intervalle normal ou acceptable. En effet, l'ensemble des informations permettant de le calculer sont disponibles sur l'écran du ventilateur. Cependant, il n'existe pas de valeur de $P_{mus,Peak}$ normale validée dans la littérature et cet indice n'est pas couramment employé pour évaluer l'effort inspiratoire du patient. En effet, la quantité d'effort respiratoire réalisée par un patient au cours du temps doit prendre en compte le temps durant lequel l'effort est soutenu. Ainsi, le produit pression-temps de l'effort musculaire inspiratoire (PTP_{mus}), qui représente l'air sous la courbe de la pression musculaire au cours du temps rapportée par minute, est un indice d'effort validé et couramment employé dans les études physiologiques au moyen de la mesure de la pression œsophagienne (2, 27,

30-33, 35, 37). Un effort respiratoire normal ou acceptable pourrait ainsi se définir par un PTP_{mus} entre 50 et 150 cm $H_2O.s.min^{-1}$ (27, 37). Cependant, le PTP_{mus} ne peut pas être calculé au lit du malade à partir des informations monitorées sur l'écran du respirateur en PAV+. Nous avons donc défini une zone cible de $P_{mus,Peak}$ considérée comme normale ou acceptable en ventilation assistée au moyen du raisonnement suivant : en faisant l'approximation que la courbe de pression musculaire est triangulaire et que l'effort inspiratoire finit au pic de pression musculaire, alors le PTP_{mus} (en cm $H_2O.s.min^{-1}$) peut être calculé ainsi (Fig. 13) :

$$PTP_{mus} = \frac{P_{mus,Peak} \times Ti}{2} \times FR \qquad [Equation\ 5]$$

Où *Ti* est le temps inspiratoire et *FR* la fréquence respiratoire.

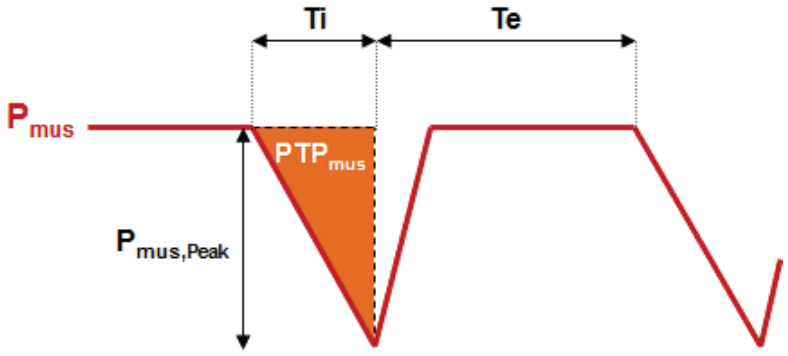

Figure 13 Estimation du produit pression temps musculaire (PTP_{mus}). En faisant l'approximation que la courbe de pression musculaire est triangulaire et que l'effort inspiratoire finit au pic de pression musculaire ($P_{mus,Peak}$), alors le PTP_{mus} (en $cmH_2O.s.min^{-1}$) peut être calculé selon l'*Equation 5*. Ti : temps inspiratoire ; Te : temps expiratoire.

A partir de l'*Equation 5*, nous avons estimé qu'avec des valeurs habituellement observées de *Ti* et *FR* en PAV+ (46, 74, 101, 102), un $P_{mus,Peak}$ entre 5 et 10 cm H_2O devrait permettre au

PTP_{mus} d'être maintenu entre 50 et 150 cm $H_2O.s.min^{-1}$. Nous avons donc considéré cette fourchette de 5 à 10 cm H_2O comme la zone cible de $P_{mus,Peak}$ lors des ajustements du gain en PAV+.

4.2. Mesure du signal EAdi et des indices d'effort respiratoire au cours de la NAVA

Pour fonctionner, la NAVA nécessite le recueil de l'EAdi au moyen d'un cathéter œsophagien muni d'électrodes positionnées en regard du diaphragme crural (68) (voir chap. 1.3.3.1). Ce cathéter dispose d'une connectique permettant de le relier au module NAVA disponible sur le ventilateur Servo-i (Maquet Critical Care, Solna, Suède). Nous avons utilisé le logiciel NAVA Tracker 2.0 (Maquet Critical Care, Solna, Suède) qui permettait d'exporter les valeurs cycle à cycle du pic d'EAdi et de l'EAdi moyen vers des fichiers Excel (Microsoft Excel, Microsoft Corporation, Redmond, WA). Afin de mesurer l'effort respiratoire réel des patients, nous avons utilisés des cathéters EAdi modifiés intégrant un ballonnet œsophagien afin de mesurer la pression œsophagienne (Fig. 14).

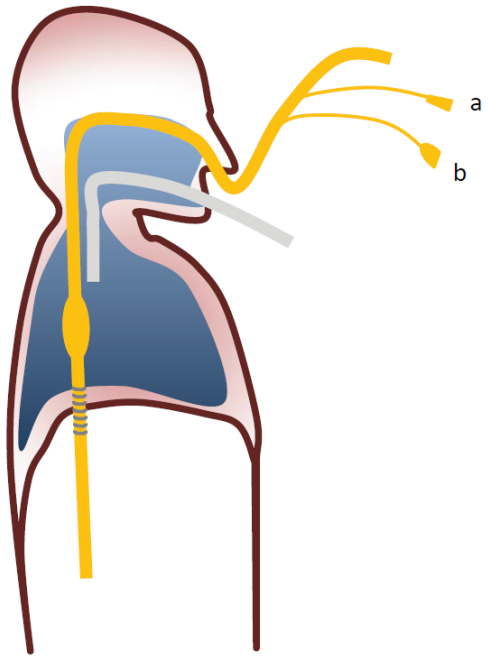

Figure 14 Représentation schématique du cathéter œsophagien muni d'un ballonnet œsophagien connecté à un capteur de pression différentielle (a) et d'électrodes recueillant le signal EAdi connectées au module NAVA du ventilateur Servo-i (b).

Le ballonnet œsophagien était connecté à un capteur de pression différentielle (Validyne MP45, ± 70 cm H_2O, Northridge, CA, USA). Sa position était vérifiée au moyen d'un test d'occlusion. Dans le même temps, nous avons recueillis les signaux de débit et de pression des voies aériennes. Le débit dans les voies aériennes a été recueilli à l'aide d'un pneumotachographe de Fleish No. 2 non chauffé inséré entre la sonde d'intubation et la pièce en Y. La pression différentielle à travers le pneumotachographe a été mesurée à l'aide de capteurs de pression différentielle (Validyne MP45, ± 2 cm H_2O, Northridge, CA, USA). La pression des voies aériennes a été obtenue à l'aide d'un capteur de pression différentielle (Validyne MP45, ± 70 cm H_2O, Northridge, CA, USA) placé entre le pneumotachographe et la sonde d'intubation. Les signaux de pression œsophagienne, de débit et de pression des voies aériennes ainsi obtenus ont été acquis en temps réel à l'aide d'un convertisseur analogique numérique (MP100 ; Biopac systems, Goleta, CA, USA) échantillonné à 200 Hz, et stockés dans un ordinateur portable pour une analyse ultérieure à l'aide du logiciel

AcqKnowledge (Biopac systems, Goleta, CA, USA). Le produit pression-temps œsophagien (*PTPes*) (30) a été calculé au moyen du logiciel SR. La courbe de pression musculaire a été construite à partir de l'équation suivante (27) (voir Fig. 15):

$$\Delta P_{mus(t)} = \Delta Pes_{(t)} + \frac{V_{(t)}}{C_{cw}} \qquad [Equation\ 6]$$

Où $\Delta Pmus_{(t)}$ est la pression musculaire générée à un instant t, $\Delta Pes_{(t)}$ et $V_{(t)}$ les deltas de pression œsophagienne et de volume à l'instant t, C_{cw} la compliance de la paroi thoracique. Chez des patients ventilant spontanément, la compliance de la paroi thoracique n'est pas mesurable, mais une estimation a été utilisée (quatre pourcent de la capacité vitale théorique) (103, 104). Le $V_{(t)}$ a été obtenu par intégration du signal de débit.

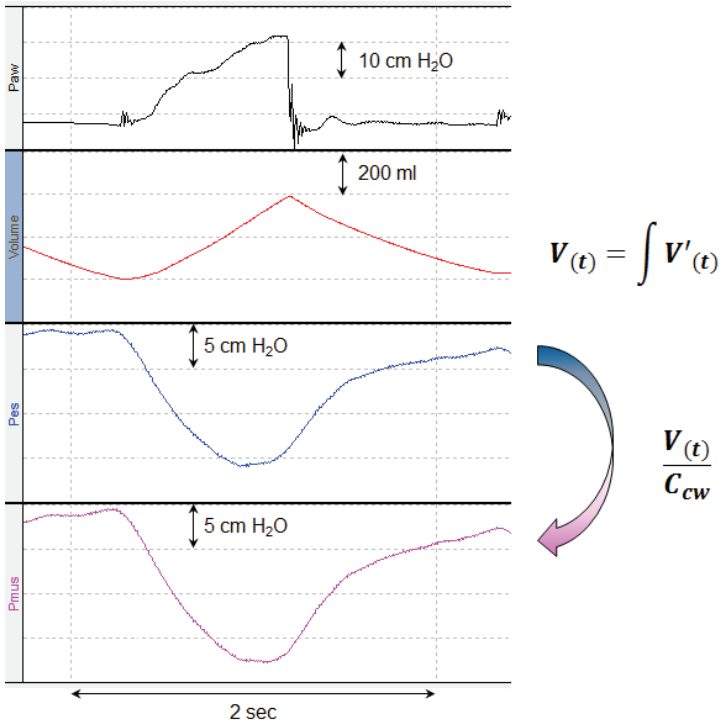

Figure 15 Construction de la courbe de pression musculaire. Le volume ($V_{(t)}$) a été calculé par intégration du signal de débit ($V'_{(t)}$). La pression musculaire a été calculée à partir des signaux de volume, de pression œsophagienne (*Pes*) et d'une estimation de la compliance de la paroi thoracique (C_{cw}) selon l'*Equation 6*. L'exemple présenté est en mode NAVA avec un niveau de NAVA réglé à 1 cm $H_2O.\mu volt^{-1}$.

Le calcul de la pression musculaire a permis de calculer le pourcentage d'assistance (% assist) – qui correspond au pourcentage de la pression totale prise en charge par le ventilateur, le pourcentage restant correspondant à la pression musculaire – comme suit :

$$\%\ assist = \frac{(P_{aw,peak} - PEP)}{(P_{aw,peak} - PEP) + P_{mus,peak}} \times 100 \qquad [Equation\ 7]$$

4.3. Détection des asynchronies en VNI à l'aide de l'électromyogramme des muscles respiratoires

La détection rigoureuse des asynchronies patient-ventilateur nécessite l'enregistrement simultané des signaux de débit et de pression dans les voies aériennes ainsi que d'un signal de l'activité musculaire inspiratoire du patient (5, 21, 22, 46, 52-55, 57, 60, 70, 78). La présence du masque en VNI et la nécessité de favoriser son étanchéité limite l'utilisation d'une sonde œsophagienne à ballonnet telle qu'elle avait été utilisée pour l'évaluation de la synchronisation patient-ventilateur chez les patients en ventilation invasive (21). Nous avons donc choisi comme signal de l'effort musculaire inspiratoire du patient l'électromyogramme (EMG) de surface du diaphragme et/ou des muscles inspiratoire du cou (principalement le scalène et/ou le sterno-cléido-mastoïdien).

Les signaux de débit et de pression des voies aériennes ont été recueillis selon les modalités décrites ci-dessus (voir chap. 4.2).

L'EMG du diaphragme a été enregistré en continu à l'aide de deux électrodes de surfaces placées au niveau du rebord costal droit sur la ligne médio-claviculaire, une électrode de référence étant placée au niveau du sternum (105). L'EMG des muscles inspiratoires du cou a été recueilli à l'aide de deux électrodes placées au niveau du triangle postérieur du cou (afin de recueillir principalement l'activité EMG du muscle scalène) ou au niveau du chef antérieur du sterno-cléido-mastoïdien (afin de recueillir principalement l'activité du muscle sterno-

cléido-mastoïdien). Le signal a été filtré et digitalisé à une fréquence d'enregistrement de 1000 hertz à l'aide du module Biopac EMG, puis rectifié et intégré.

L'analyse simultanée des tracés de débit et de pression des voies aériennes ainsi que des tracés EMG des muscles inspiratoires permettait de repérer et de caractériser l'ensemble des asynchronies majeures patient-ventilateur précédemment décrites (22, 24) (Fig. 1 et 16).

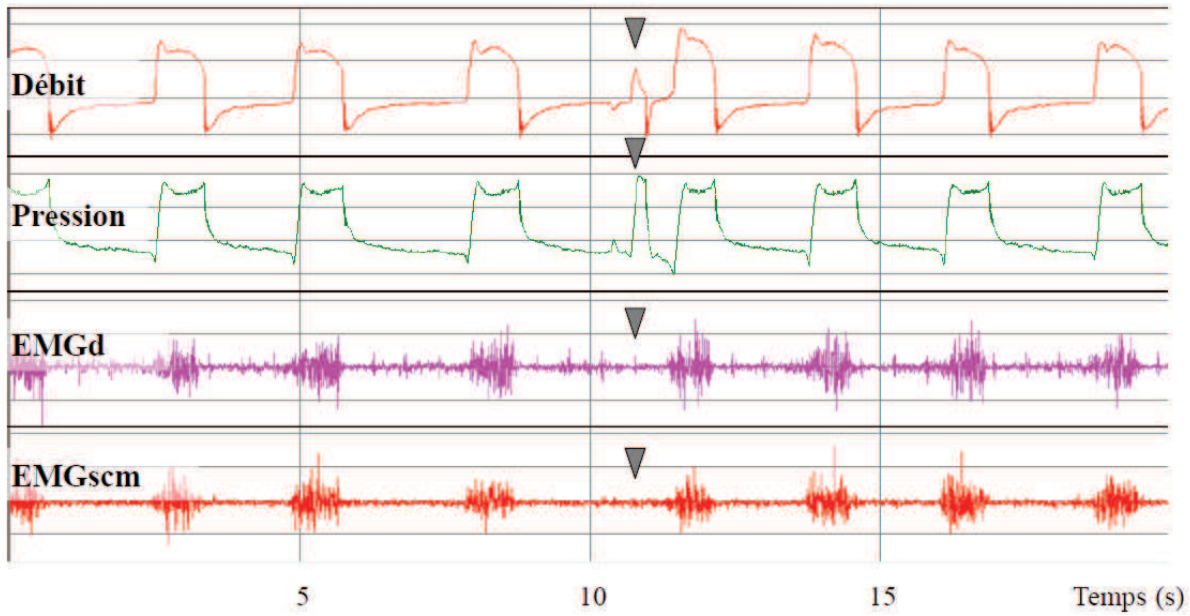

Figure 16 Auto-déclenchement en VNI. Les courbes représentent (de haut en bas) : le débit dans les voies aériennes, la pression des voies aériennes, l'EMG du diaphragme (EMGd) et l'EMG du sterno-cléido-mastoïdien (EMGscm). Les flèches grises pointent un cycle d'allure tronquée, délivré par le ventilateur mais non déclenché par un effort inspiratoire du patient (pas d'activité EMG), il s'agit d'un auto-déclenchement.

4.4. Description d'un modèle expérimental reproduisant les différentes conditions de fuites susceptibles de générer des asynchronies en VNI

Afin de reproduire les différentes conditions de fuites qui sont à même de perturber les signaux habituellement utilisés par les ventilateurs pour synchroniser leur assistance à l'effort inspiratoire du patient nous avons conçu un modèle sur banc d'essai simple et reproductible générant de manière distincte des fuites expiratoires et des fuites inspiratoires.

Pour simuler l'effort inspiratoire du patient, nous avons utilisé un Active Servo Lung 5000 (ASL 5000; Ingmar Medical, Pittsburgh, Pennsylvania). La compliance et les résistances simulées du système respiratoire étaient respectivement de 80 ml.cm H_2O^{-1} et 10 cm $H_2O.l.s^{-1}$. La pression musculaire simulée avait un aspect trapézoïde afin de se rapprocher d'un effort respiratoire tel qu'observé chez des patients. Le pic de pression musculaire était de 6.5 cm H_2O, ce qui représente un effort respiratoire modéré, le temps inspiratoire était de 0.8s, et la fréquence respiratoire de 15/min (Fig. 17).

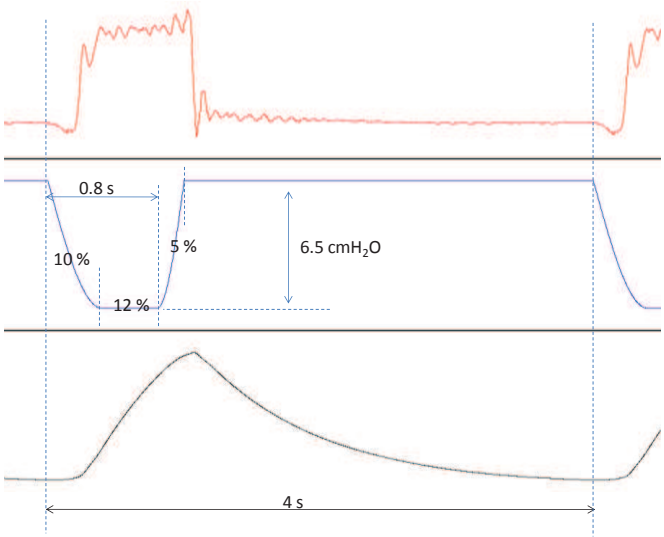

Figure 17 Simulation de la pression musculaire avec le poumon test ASL5000: Les courbes représentent (de haut en bas) : la pression dans le circuit, la pression musculaire simulée, le volume. La forme de la pression musculaire simulée était trapézoïde avec un pic de pression musculaire à 6.5 cmH_2O et un temps inspiratoire de 0.8 s.

Les différentes fuites ont été générées en insérant en série au moyen d'une pièce en T sur la branche inspiratoire du circuit du respirateur une bouteille comportant une seconde ouverture qu'il était possible d'obturer au moyen d'un bouchon. Les Fig. 18-20 ci-dessous détaillent ce modèle expérimental.

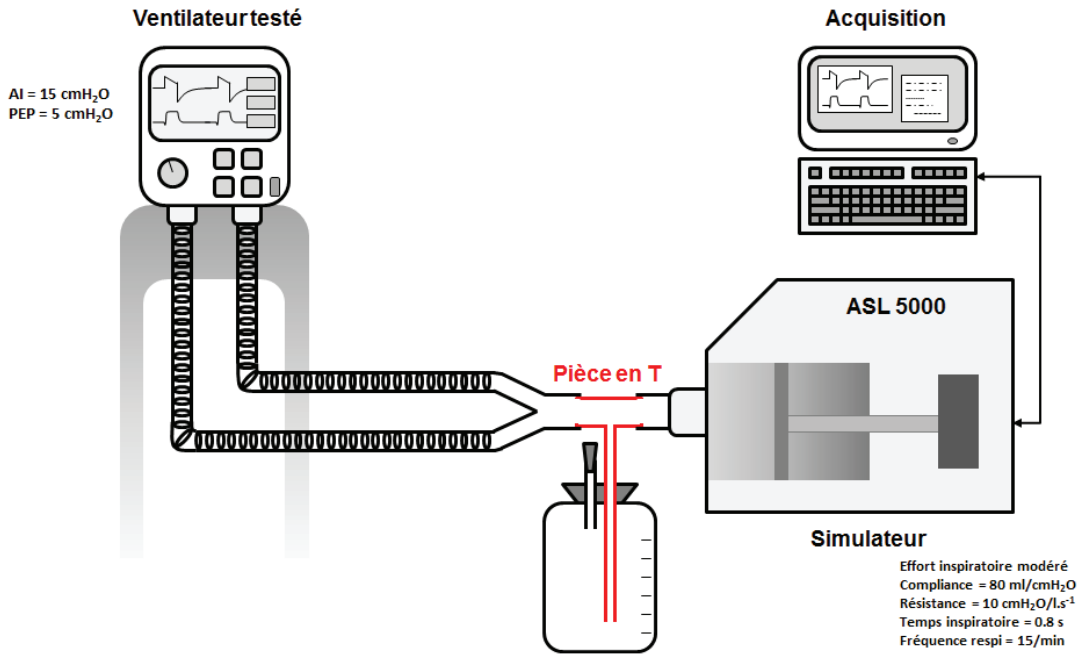

Figure 18 Modèle expérimental utilisé pour générer différentes conditions de fuites en VNI. Lorsque le bouchon obstrue la deuxième ouverture de la bouteille connectée en série sur le circuit du respirateur au moyen d'une pièce en T, aucune fuite n'est générée. Cette situation simule des conditions invasives sans fuites.

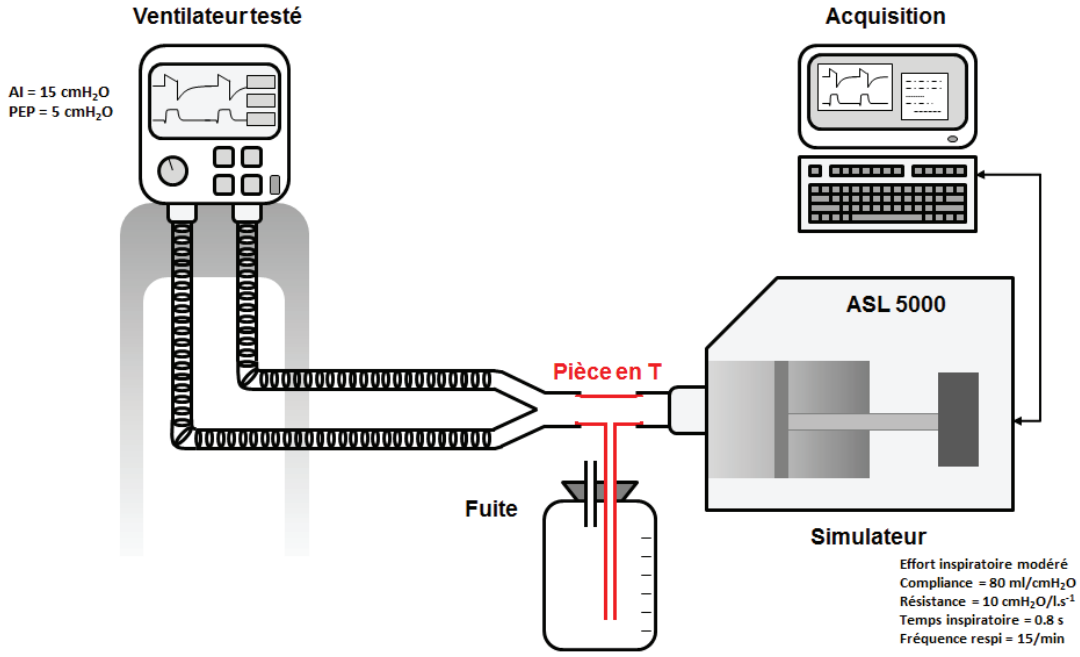

Figure 19 Modèle expérimental utilisé pour générer différentes conditions de fuites en VNI. Lorsque la deuxième ouverture de la bouteille connectée en série au circuit du respirateur est ouverte, il existe une fuite permanente. Cette condition permettait l'étude de la survenue d'auto-déclenchement au cours du temps expiratoire.

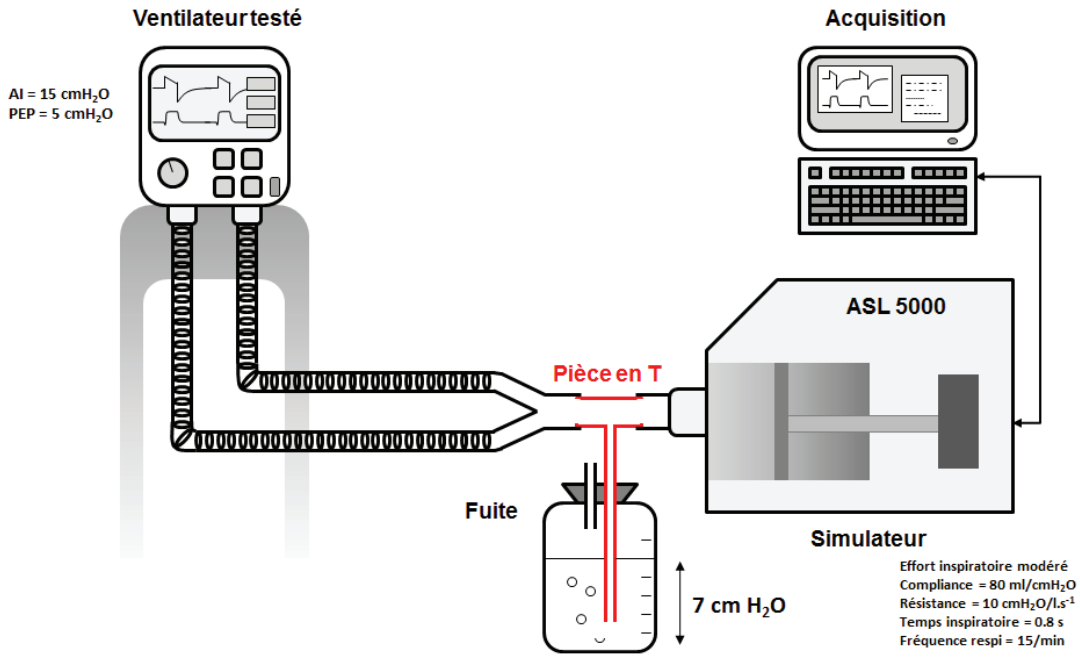

Figure 20 Modèle expérimental utilisé pour générer différentes conditions de fuites en VNI. Lorsque la bouteille connectée en série sur le circuit du respirateur était remplie d'eau sur une hauteur de 7 cm, les fuites survenaient lorsque la pression dans le circuit du respirateur dépassait 7 cm H_2O. La PEP étant réglée à 5 cm H_2O et la pression d'aide inspiratoire à 15 cm H_2O, la fuite survenait donc en cours d'insufflation du ventilateur. Cette condition permettait d'étudier la survenue d'insufflation prolongée au cours des fuites inspiratoires.

Ce modèle standardisé et reproductible permettait d'évaluer la synchronisation patient ventilateur dans différentes conditions de fuite sur différents ventilateurs : ventilateurs de réanimation avec ou sans l'algorithme VNI enclenché, ventilateurs dédiés à la VNI ou encore ventilateurs de transport.

5. RESULTATS ET DISCUSSION DES ETUDES

1) Carteaux G, Mancebo J, Mercat A, Dellamonica J, Richard JC, Aguirre-Bermeo H, Kouatchet A, Beduneau G, Thille AW, Brochard L. Bedside adjustment of proportional assist ventilation to target a predefined range of respiratory effort. Crit Care Med. 2013 Sep;41(9):2125-32.

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4) Carteaux G, Lyazidi A, Cordoba-Izquierdo A, Vignaux L, Jolliet P, Thille AW, Richard JC, Brochard L. Patient-ventilator asynchrony during noninvasive ventilation: a bench and clinical study. Chest. 2012 Aug;142(2):367-76.

Article 1 :

Evaluation de la faisabilité clinique d'ajuster le mode PAV+ avec pour but de maintenir l'effort respiratoire du patient dans une zone normale

Bedside Adjustment of Proportional Assist Ventilation to Target a Predefined Range of Respiratory Effort*

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Objectives: During proportional assist ventilation with load-adjustable gain factors, peak respiratory muscle pressure can be estimated from the peak airway pressure and the percentage of assistance (gain). Adjusting the gain can, therefore, target a given level of respiratory effort. This study assessed the clinical feasibility of titrating proportional assist ventilation with load-adjustable gain factors with the goal of targeting a predefined range of respiratory effort.

Design: Prospective, multicenter, clinical observational study.

Settings: Intensive care departments at five university hospitals.

Patients: Patients were included after meeting simple criteria for assisted mechanical ventilation.

Interventions: Patients were ventilated in proportional assist ventilation with load-adjustable gain factors. The peak respiratory muscle pressure, estimated in cm H_2O as (peak airway pressure − positive end-expiratory pressure) × [(100 − gain)/gain], was calculated from a grid at the bedside. The gain adjustment algorithm was defined to target a peak respiratory muscle pressure between 5 and 10 cm H_2O. Additional recommendations were available in case of hypoventilation or hyperventilation.

Results: Fifty-three patients were enrolled. Median time spent under proportional assist ventilation with load-adjustable gain factors was 3 days (interquartile range, 1–5). Gain was adjusted 1.0 (0.7–1.8) times per day, according to the peak respiratory muscle pressure target range in 91% of cases and because of hypoventilation or hyperventilation in 9%. Thirty-four patients were ventilated with proportional assist ventilation with load-adjustable gain factors until extubation, which was successful in 32. Eighteen patients required volume assist-controlled reventilation because of clinical worsening and need for continuous sedation. One patient was intolerant to proportional assist ventilation with load-adjustable gain factors.

Conclusions: This first study assessing the clinical feasibility of titrating proportional assist ventilation with load-adjustable gain factors in an attempt to target a predefined range of effort showed that adjusting the level of assistance to maintain a predefined boundary of respiratory muscle pressure is feasible, simple, and often sufficient to ventilate patients until extubation. (*Crit Care Med* 2013;41:2125–2132)

Key Words: algorithms; assisted mechanical ventilation; proportional assist ventilation; respiratory muscles; ventilator weaning

*See also p. 2230.

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One of the main goals of assisted mechanical ventilation is to decrease the patient's respiratory effort (1) while maintaining some respiratory muscle activity. This approach not only reduces dyspnea and signs of respiratory distress but may also prevent the rapid respiratory muscle atrophy observed during controlled mechanical ventilation (2) and the resulting ventilator-induced diaphragmatic dysfunction (3–7). It also helps to reduce the deleterious effects of prolonged sedation (8, 9). To reach such goals, however, the amount of assistance should theoretically be adjusted to target normal or reasonable levels of respiratory effort. Unfortunately, measures of respiratory effort are not available for routine bedside use, except during physiological studies. Adjusting ventilator settings during assisted modes is, thus, a clinical challenge, associated with hazards for the patient.

Proportional assist ventilation with load-adjustable gain factors (PAV+) is a ventilatory mode that delivers assistance in proportion to the instantaneous flow and volume, calculating the instantaneous pressure needed to overcome the elastic and resistive pressures. This is done by performing automated and repeated measurements of compliance and resistance of the respiratory system (10–12). Thus, assistance is expressed as a percentage of the total pressure needed to inflate the chest. This percentage, called the gain, is adjusted by the clinician. Because of its unique working principles, PAV+ allows to estimate the pressure generated by the respiratory muscles. Such an estimate can easily be done at the bedside from the values of the gain and the driving inspiratory airway pressure. By adjusting the gain, one can obtain a known level of respiratory muscle effort. We, therefore, designed a simple algorithm to adjust the gain during PAV+ in order to target a reasonable and predefined range of respiratory muscle pressure.

The aim of this study was to assess whether such an algorithm could be implemented safely and effectively to ventilate patients with PAV+ from the start of assisted ventilation until ventilator withdrawal.

MATERIALS AND METHODS

An extensive description of the methods is provided in the **supplemental data** (Supplemental Digital Content 1, http://links.lww.com/CCM/A649).

This was a prospective, multicenter observational study involving five university hospitals, four in France (Angers, Créteil, Nice, Rouen) and one in Spain (Barcelona). The study was approved by the Ethics Committee of the Société de Réanimation de Langue Française (French Society of Intensive Care Medicine) and the Ethics Committee of the Sant Pau Hospital, Barcelona.

Patients

Patients were prospectively included while ventilated in assist control ventilation (ACV) as soon as the following criteria were met: ability to trigger every ventilator cycle, plateau pressure below 30 cm H_2O with a tidal volume of 6–8 mL/kg of predicted body weight, positive end-expiratory pressure (PEEP) level ≤ 10 cm H_2O, PaO_2/FIO_2 > 150 or SaO_2 ≥ 90% with FIO_2 ≤ 50%, stable hemodynamic status with or without a moderate dose of vasopressor (epinephrine or norepinephrine ≤ 2 mg/hr), body temperature between 36°C and 39°C, and Richmond Agitation Sedation Scale score ≥ −4 (13). Patients were not included in case of age below 18 yr, pregnancy, "do not resuscitate" order or expected poor short-term prognosis, pneumothorax or chest tube with a suspicion of bronchopleural fistula, or prolonged cardiac arrest with poor neurological prognosis.

Measurements

Demographic, hemodynamic, and respiratory data, arterial blood gases and the Richmond Agitation Sedation Scale score were recorded at inclusion under ACV and daily under PAV+.

A laptop PC was connected to the ventilator, using a dedicated software that recorded the following parameters every minute over the whole duration of PAV+ ventilation: FIO_2, PEEP, gain, peak airway pressure ($P_{aw,Peak}$), mean airway pressure ($P_{aw,Mean}$), respiratory rate (RR), expired tidal volume (Vte), and insufflation time (Ti).

Gain Adjustment Rules During PAV+

Patients were ventilated with PAV+ using a Puritan-Bennett 840 ventilator (Covidien, Galway, Ireland) until either extubation or the need to change the ventilatory mode.

The protocol to adjust the gain during PAV+ ventilation was designed to maintain the patient within a reasonable targeted range of respiratory effort, which we defined as a respiratory muscle pressure–time product (PTP_{mus}) between 50 and 150 cm H_2O·s/min (1, 14). As it was not feasible to directly calculate the PTP_{mus} at the bedside, we used its major component as a surrogate: the peak muscle pressure of the respiratory muscles ($P_{mus,Peak}$). This pressure is the maximum swing made by the inspiratory muscles during inspiration, and it can be estimated breath by breath using the following equation:

$$P_{mus,Peak} = (P_{aw,Peak} - PEEP) \times \frac{100 - Gain}{Gain} \quad (1)$$

where $P_{aw,Peak}$ is the peak airway pressure.

A grid built from this equation was available at the bedside (**Fig. 1**), allowing the rapid estimate of the $P_{mus,Peak}$. From the values of the gain, the PEEP, and the $P_{aw,Peak}$, which all are available on the screen of the ventilator, the $P_{mus,Peak}$ can be immediately estimated.

By assuming that the muscle pressure (P_{mus}) waveform has a triangular shape with the end of the inspiratory effort at the $P_{mus,Peak}$, the PTP_{mus}, which represents the area under the P_{mus} curve during the inspiratory time, could be estimated over a minute (in cm H_2O·s/min) as follows (**Fig. 2**):

$$PTP_{mus} = \frac{P_{mus,Peak} \times Ti}{2} \times RR \quad (2)$$

where Ti is the inspiratory time and RR the respiratory rate.

From this estimation of the PTP_{mus}, we considered that with usual values of Ti and RR (15–18), targeting a $P_{mus,Peak}$ between 5 and 10 cm H_2O should allow the PTP_{mus} to remain between 50 and 150 cm H_2O·s/min. We then designed a simple algorithm,

Gain (percentage of assistance)	Delta P_{aw} (cm H_2O) = $P_{aw,Peak}$ – PEEP																					
	1	2	3	4	5	6	7	8	9	10	12	15	17	20	22	25	27	30	32	35	37	40
20	4	8	12	16	20	24	28	32	36	40	48	60	68	80	88	100	108	120	128	140	148	160
25	3	6	9	12	15	18	21	24	27	30	36	45	51	60	66	75	81	90	96	105	111	120
30	2	5	7	9	12	14	16	19	21	23	28	35	40	47	51	58	63	70	75	82	86	93
35	2	4	6	7	9	11	13	15	17	19	22	28	32	37	41	46	50	56	59	65	69	74
40	2	3	5	6	8	9	11	12	14	15	18	23	26	30	33	38	41	45	48	53	56	60
45	1	2	4	5	6	7	9	10	11	12	15	18	21	24	27	31	33	37	39	43	45	49
50	1	2	3	4	5	6	7	8	9	10	12	15	17	20	22	25	27	30	32	35	37	40
55	1	2	2	3	4	5	6	7	7	8	10	12	14	16	18	20	22	25	26	29	30	33
60	1	1	2	3	3	4	5	5	6	7	8	10	11	13	15	17	18	20	21	23	25	27
65	1	1	2	2	3	3	4	4	5	5	6	8	9	11	12	13	15	16	17	19	20	22
70	0	1	1	2	2	3	3	3	4	4	5	6	7	9	9	11	12	13	14	15	16	17
75	0	1	1	1	2	2	2	3	3	3	4	5	6	7	7	8	9	10	11	12	12	13
80	0	1	1	1	1	2	2	2	2	3	3	4	4	5	6	6	7	8	8	9	9	10
85	0	0	1	1	1	1	1	1	2	2	2	3	3	4	4	4	5	5	6	6	7	7
90	0	0	0	0	1	1	1	1	1	1	1	2	2	2	2	3	3	3	4	4	4	4

Figure 1. Peak muscle pressure of the respiratory muscles ($P_{mus,Peak}$) grid. Grid giving the value of the $P_{mus,Peak}$ from the values of the peak airway pressure ($P_{aw,Peak}$), the positive end-expiratory pressure (PEEP), and the percentage of assistance (Gain), using the following equation: $P_{mus,Peak} = (P_{aw,Peak} - \text{PEEP}) \times \frac{100 - \text{Gain}}{\text{Gain}}$. This grid was available at the bedside and was used to adjust the gain in PAV+ (Fig. 3). The white area corresponds to the $P_{mus,Peak}$ target range (5 cm $H_2O \le P_{mus,Peak} \le$ 10 cm H_2O).

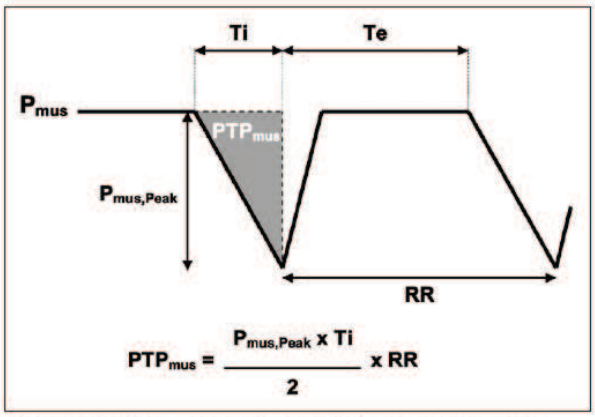

Figure 2. Estimation of the respiratory muscles pressure (P_{mus})–time product (PTP_{mus}). By considering that the muscle pressure waveform had a triangular shape with the end of the inspiratory effort at the $P_{mus,Peak}$, the PTP_{mus}, which represents the area under the P_{mus} curve during the inspiratory time, could be calculated over a minute (in cm H_2O·s/min) as follows: $PTP_{mus} = \frac{P_{mus,Peak} \times \text{inspiratory time (Ti)}}{2} \times \text{respiratory rate (RR)}$. This estimation was used to define the target range of $P_{mus,Peak}$ between 5 and 10 cm H_2O, assuming that with usual values of Ti and RR, this should allow the PTP_{mus} to remain between 50 and 150 cm H_2O·s/min. The same equation was used to calculate the time spent in each PTP_{mus} range (<50, between 50 and 150, >150 cm H_2O·s/min) from the data recorded every minute in 45 patients. Te = expiratory time; $P_{mus,Peak}$: peak muscle pressure of the respiratory muscles.

described in Fig. 3, that primarily aimed at keeping the $P_{mus,Peak}$ between 5 and 10 cm H_2O ($P_{mus,Peak}$ target range).

Briefly, we first defined some "standard P_{mus}-settings" that only took into account this target range of $P_{mus,Peak}$ to adjust the gain during PAV+ and that had to be used first. We also defined "additional settings" that had to be used in case of hypoventilation or hyperventilation observed despite a $P_{mus,Peak}$ within the target range. Both the FIO_2 and the PEEP were set according to the standard practice in each participating center. Patients were assessed every 8 hrs, or more frequently if needed, to adjust the ventilator settings. The study was ended either after extubation or when there was a need to switch back to ACV. Criteria for switching back to ACV were as follows: the need to increase the gain above 85%, the FIO_2 above 70%, or the PEEP above 10 cm H_2O, and the need for prolonged continuous sedation. Withdrawal from mechanical ventilation was based on daily screening followed by a weaning trial performed with 7 cm H_2O pressure support ventilation and zero PEEP. PAV+ gain was not used as an indicator of weaning capacity. Except for the ventilator settings, medical management did not differ from routine care.

Data Analysis

Each gain adjustment was classified whether it was made according to the P_{mus}-setting rules or additional setting rules.

The data recorded every minute in the laptops connected to the ventilators, especially the Ti, RR, $P_{aw,Peak}$, gain, and PEEP, allowed to calculate the percentage of the time spent in each range of PTP_{mus} (<50, between 50 and 150, >150 cm H_2O·s/min) from Equation 2.

Statistics

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 16.0, Chicago, IL). Continuous data are expressed as the median (25th, 75th percentile). Comparisons between patients who were and were not extubated at the end of the PAV+ ventilation were made using a Mann-Whitney *U* test. Comparisons among paired variables were made using a Wilcoxon signed-rank test. A two-sided *p*-value of 0.05 or less was considered statistically significant.

RESULTS

Population

Fifty-three patients were included. Their main demographic and clinical characteristics at enrolment are reported in **Table 1**. Their respiratory parameters under ACV before starting PAV+ and at PAV+ inclusion are shown in **Table 2**. Technical problems precluded the use of the laptop PC for data acquisition in eight patients.

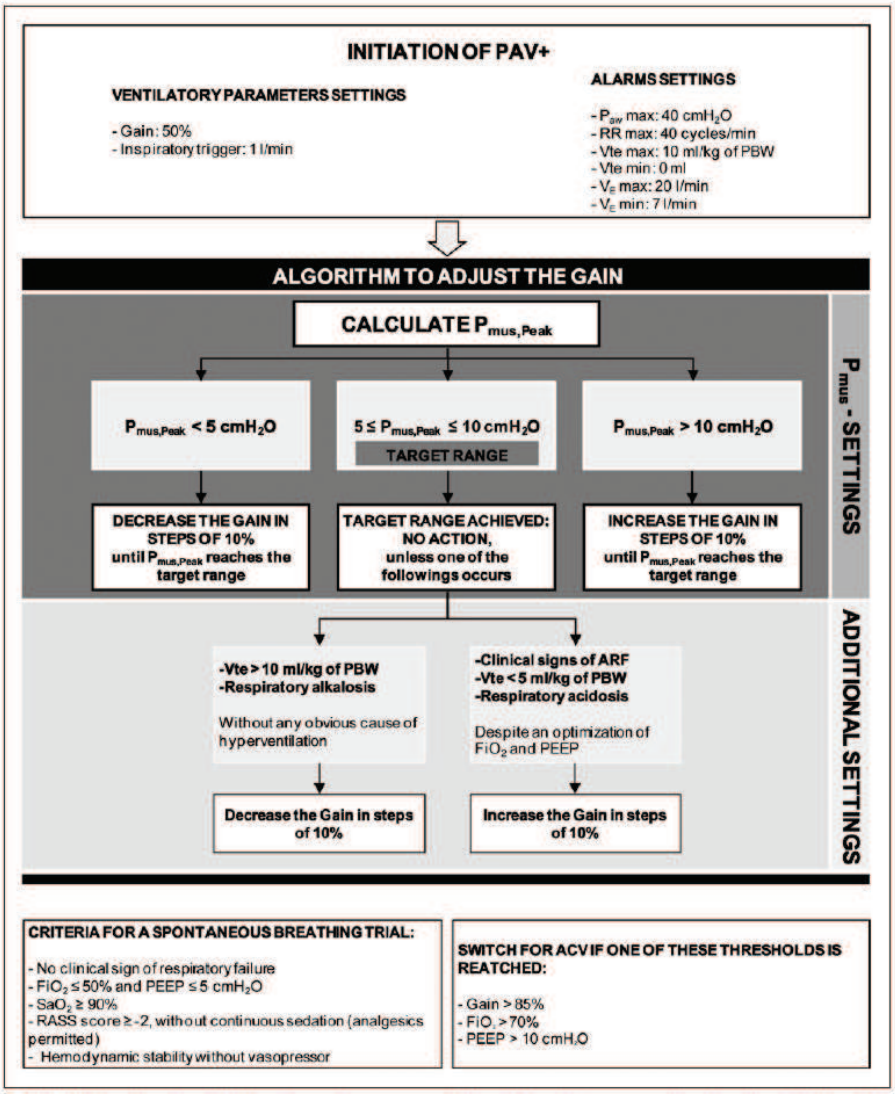

Figure 3. Algorithm to adjust the gain and manage ventilator settings during proportional assist ventilation with load-adjustable gain factors (PAV+). P_{aw} = airway pressure, RR = respiratory rate, Vte = expired tidal volume, V_E = minute ventilation, $P_{mus,Peak}$ = peak muscle pressure of the respiratory muscles, ARF = acute respiratory failure, PEEP = positive end-expiratory pressure, RASS = Richmond agitation sedation scale. The $P_{mus,Peak}$ was calculated using the grid represented Figure 1.

Feasibility and Compliance With the Protocol

In all but one patient, the protocol succeeded in maintaining the $P_{mus,Peak}$ within the target range. The total number of gain adjustments in the 53 patients amounted to 247 (Table 3). The median number of gain adjustments per patient per day was 1.0 (0.7, 1.8). Among the 247 gain adjustments, the P_{mus}-settings were used 225 times (91%) to target the $P_{mus,Peak}$ between 5 and 10 cm H_2O; six of these adjustments (2%) deviated modestly from the protocol because they were made in steps of 5% rather than 10% as defined in the protocol. No other protocol deviation was recorded. Additional settings were used in 22 instances (9%) and concerned 12 patients (23%), representing 29% (17, 33) of the total adjustments that these 12 patients required. Reasons for using additional settings are reported in Table 3.

PTP_{mus} Range

Based on the analysis of the minute-by-minute recordings of the ventilatory data (n = 45), patients spent 79% (64, 85) of their time with a PTP_{mus} between 50 and 150 cm H_2O·s/min, 3% (2, 8) with a PTP_{mus} less than 50 cm H_2O·s/min, and 15% (8, 25) with a PTP_{mus} over 150 cm H_2O·s/min.

Respiratory Parameters Under PAV+

Table 4 shows the mean values of respiratory parameters recorded in 45 patients during PAV+ ventilation, as well as their minute-by-minute coefficient of variation. Concerning tidal volume, patients spent 27% (2, 43) of their time with a Vte less than 6 mL/kg, 57% (37, 69) with a Vte between 6 and 8 mL/kg, and 16% (3, 31) with a Vte higher than 8 mL/kg.

Patient Outcome

Patients spent 3 days (1, 5) under PAV+. Thirty-four patients were extubated, and two of them required reintubation within the next 48 hrs (6%). Sixteen had failed the first weaning trial before extubation. The median gain was not significantly different in case of success and failure of the weaning trial: 48% (35, 59) and 50% (40, 60), respectively, $p = 0.189$. In 31 of these 34 patients ventilated with PAV+ until first extubation (91%), 100% of the gain adjustments had been made according to the P_{mus}-settings. In the remaining 19 patients, ventilation with ACV was resumed. These latter patients had a higher SAPS II at inclusion (42 [37, 50] vs 34 [27, 41]; $p = 0.02$) and had spent more days under ACV before inclusion (6 d [5, 9] vs 4 [2, 6]; $p = 0.01$). All files were carefully analyzed to determine the reason for switching back to ACV. The main reasons for switching to ACV were clinical worsening requiring continuous sedation in 18 patients and the need to increase the gain to above 85% in one patient. This last patient had a metabolic acidosis and was eventually weaned successfully under pressure support ventilation.

TABLE 1. Patient Demographic and Clinical Characteristics at Enrollment

n	53
Male:female	40:13
Age, median (IQR)	67 (57, 74)
Body mass index, median (IQR)	27 (25, 33)
SAPS II at ICU admission, median (IQR)	52 (40, 63)
SAPS II at inclusion, median (IQR)	37 (28, 44)
Richmond Agitation Sedation Scale at inclusion, median (IQR)	−1 (−3, 0)
Chronic conditions, *n* (%)	
COPD	12 (23)
Restrictive pulmonary disease	1 (2)
Obesity hypoventilation syndrome	5 (9)
Hypertension	21 (40)
Chronic heart failure	15 (28)
Chronic renal failure	11 (21)
Liver cirrhosis	8 (15)
Main reason for mechanical ventilation, *n* (%)	
Acute lung injury/acute respiratory distress syndrome	20 (38)
Exacerbation of COPD	3 (6)
Sepsis/septic shock	11 (21)
Congestive heart failure	1 (2)
Cardiac arrest	1 (2)
Hemorrhagic shock	2 (4)
Nontraumatic disease of the central nervous system	4 (8)
Postsurgery	6 (11)
Other	5 (9)
Number of days spent under assist control ventilation before inclusion, median (IQR)	5 (3, 7)

IQR = interquartile range, SAPS II = Simplified Acute Physiology Score, COPD = chronic obstructive pulmonary disease.

DISCUSSION

This is the first study in which the level of assistance was individually adjusted to target each patient's respiratory effort. It is also the first report to include patients who were ventilated with PAV+ from the start of partial ventilatory support until the moment of extubation.

Targeting the Patient's Respiratory Effort to Adjust the Gain

As unloading the respiratory muscles is the first aim of assisted mechanical ventilation (1), adjusting the level of assistance to target a predefined range of patient's respiratory effort seems highly desirable. However, the direct measure of the respiratory muscle pressure is not possible in clinical practice. Using common modes of assisted mechanical ventilation, such as ACV or pressure support ventilation (PSV) (19), such a direct measure would require measurement of the esophageal pressure and calculation of the chest wall compliance (14). Furthermore, any modification in the level of assistance during PSV alters both the respiratory effort (20) and the respiratory pattern (Vte, Ti, RR) (16), making it difficult to optimize patient–ventilator interactions (21).

With proportional assist ventilation, the level of gain minimally influences tidal volume (16) and keeps insufflation time very close to the neural inspiratory time (22). With this mode, patients freely maintain their own respiratory pattern and minute ventilation. Modifying the gain, therefore, mainly alters the respiratory effort. Consequently, setting the gain in PAV+ to target a predefined reasonable range of respiratory effort makes sense in terms of patient–ventilator interactions and physiological effects. Unlike ACV and PSV, PAV+ uses the equation of motion of the respiratory system as a working principle (23). Peak pressure performed by the respiratory muscles can, therefore, be calculated at the bedside ($P_{mus,Peak}$) (24). Kondili et al (25) showed that during PAV+, estimating muscle pressure from flow and airway pressure signals and respiratory mechanics using the equation of motion was accurate.

In this study, we designed an algorithm aiming to maintain the $P_{mus,Peak}$ between 5 and 10 cm H_2O because we estimated that this should allow the PTP_{mus} to remain between 50 and 150 cm H_2O·s/min. Jubran et al (14) showed that—assuming dynamic hyperinflation was absent—the PTP of the respiratory muscles was 141 ± 21 cm H_2O·s/min at the beginning and 180 ± 22 cm H_2O·s/min at the end of a successful weaning trial with a T-tube. It has also been reported that in difficult to wean patients, a weaning trial made using a T-tube required more respiratory effort than a trial using PSV with a pressure level at 7 cm H_2O and no PEEP (26). In contrast, a PTP_{mus} less than 40 cm H_2O·s/min is considered by some authors as excessive muscle unloading, raising fears about muscle injury (1). We, therefore, hypothesized that a PTP_{mus} between 50 and 150 cm H_2O·s/min should represent an acceptable and reasonable range of respiratory effort during assisted mechanical ventilation for most patients. Although this range is reasonable, it may not suit some subgroups of patients who have a different basal work of breathing and should be refined by further research. Furthermore, the optimal target effort may vary from patient to patient, even within our target range. Our algorithm allowed the PTP_{mus} to remain within the target range for 79% (64, 85) of the time and required only 1.0 (0.7, 1.8) adjustment of the gain per day. For comparison, Dojat et al (27) reported that adjusting pressure support levels 1 ± 2 times per day maintained patients in a predefined zone of respiratory comfort for 66% ± 23% of the time . In the same study, a computer-driven system to automatically

TABLE 2. Respiratory Parameters at Inclusion

Parameter	Under Assist-Control Ventilation, Before PAV+	Under PAV+, After Stabilization	p
Pao_2/Fio_2, mm Hg	207 (170, 260)	235 (169, 292)	0.08
Fio_2, %	40 (35, 50)	40 (30, 50)	0.32
Positive end-expiratory pressure, cm H_2O	5 (5, 6)	5 (5, 6)	0.71
Expired tidal volume, mL/kg	6.7 (6.3, 7.3)	6.9 (6.0, 8.9)	0.12
Respiratory rate, cycle/min	26 (21, 29)	25 (20, 31)	0.83
Minute ventilation, L/min	10.8 (8.9, 12.9)	10.4 (8.6, 13.7)	0.58
Static compliance, mL/cm H_2O	36 (32, 44)		
Resistance, cm H_2O/L/s	14 (9, 16)		
P0.1, cm H_2O	1.6 (0.9, 3.4)	2.9 (1.8, 4.4)	0.01
Gain (percentage of assistance), %		50 (50, 60) [20–80]	
pH	7.44 (7.39, 7.46)	7.42 (7.38, 7.46)	0.32
Pao_2, mm Hg	80 (71, 98)	83 (73, 99)	0.15
$Paco_2$, mm Hg	38 (33, 42)	39 (34, 42)	0.36

PAV+ = proportional assist ventilation with load-adjustable gain factors.
Results are given in median (25th, 75th percentile) [minimum value–maximum value].

adjust the pressure support level kept the patients within the comfort zone 93% ± 8% of the time, and assistance was adjusted 56 ± 40 times per day (27). Taking these findings into account, we contend that our algorithm is simple and should be easy to implement in other ICUs.

PAV+ Ventilation in Clinical Practice

Using a target range of $P_{mus,Peak}$ to adjust the gain, we have shown that it is feasible to ventilate patients with PAV+ throughout the duration of partial ventilatory support, without any significant adverse event. In a randomized clinical study, Xirouchaki et al (28) reported the feasibility of using PAV+ compared with PSV for 48 hours. At the end of these 48 hours, the failure rate (i.e., the need to switch to controlled modes) was significantly lower in patients ventilated with PAV+ (11%) than in patients ventilated with PSV (22%).

Our study design did not allow comparison with another ventilatory mode or with other approaches using PAV+, such as gradually decreasing the proportion of ventilatory assistance. Although our algorithm is feasible, comparative studies with routine practice are needed. It is important to note that in accordance with standard practice (29), weaning trials were performed in our study regardless of the level of assistance. The gain at the time of extubation ranged from 25% to 75%,

TABLE 3. Gain Adjustments and Adherence to the Protocol During Proportional Assist Ventilation With Load-Adjustable Gain Factors

Total number of gain adjustments (53 patients), *n*	247
Number of gain adjustment per day, median (interquartile range)	1.0 (0.7, 1.8)
Gain adjustments made accordingly to the P_{mus}-settings[a], *n* (%)	225 (91)
Gain adjustments made accordingly to the additional settings[a], *n* (%)	22 (9)
Main reason for additional settings use, *n*	
Clinical signs of respiratory distress	4
Vte < 5 mL/kg	3
Respiratory acidosis	1
Vte > 10 mL/kg	4
Respiratory alkalosis	10

Vte = expired tidal volume.
[a]See Figure 3 and *Patients* section for definitions.

TABLE 4. Respiratory Parameters Under Proportional Assist Ventilation With Load-Adjustable Gain Factors ($n = 45$)

	Mean Value During PAV+ Ventilation	Minute-by-Minute Coefficient of Variation (%)
Expired tidal volume	6.8 mL/kg (6.1, 8.0)	21 (15, 28)
Insufflation time	0.9 s (0.8, 1.0)	20 (19, 33)
Respiratory rate	26 cycles/min (24, 30)	13 (11, 16)
Minute ventilation	10.6 L/min (9.5, 13.4)	15 (13, 19)
Peak airway pressure – positive end-expiratory pressure	10 cm H_2O (8, 17)	25 (20, 30)
Mean airway pressure	10 cm H_2O (8, 11)	10 (6, 14)
Muscle pressure–time product	108 cm H_2O·s/min (96, 132)	41 (37, 49)

PAV+ = proportional assist ventilation with load-adjustable gain factors.
Results are given in median (25th, 75th percentile).

and differences between weaning trial successes and failures were not significant.

Eighteen patients needed to be switched back to ACV due to clinical worsening, and continuous sedation was required. This proportion is consistent with recent multicenter studies in the field of weaning and conducted using PSV (30, 31).

One patient in our study did not tolerate the PAV+ mode and was switched to ACV. This patient had metabolic acidosis and his $P_{mus,Peak}$ remained above 10 cm H_2O even though the gain was increased above 85% during PAV+. This clinical scenario raises some questions about how to select the patients who could benefit from PAV+. Because the assistance delivered during PAV+ is in proportion to the patient's respiratory effort, patients with a high respiratory drive not related to the load per se (e.g., patients with metabolic acidosis or central nervous system diseases) may not be good candidates for PAV+, especially if the assistance is adjusted according to the respiratory effort. Although overdistension has not been reported with PAV+—even at high levels of assistance (16, 28)—clinicians should be aware that PAV+ may amplify an abnormal respiratory drive that is not related to the load per se.

Limitations

Our calculation of the $P_{mus,Peak}$ did not take into account the possible presence of an intrinsic PEEP (PEEPi). The value of the $P_{mus,Peak}$ could, therefore, have been underestimated in some patients. However, because tidal volume is chosen by the patient on a breath-by-breath basis (23) and the insufflation time is close to the neural inspiratory time (23, 32) whatever the level of assistance (16), the risk of significant dynamic hyperinflation is low in PAV+ (22). Furthermore, Appendini et al (15) showed that adding continuous positive airway pressure during proportional assist ventilation dramatically reduced the level of PEEPi in chronic obstructive pulmonary disease (COPD) patients with a high basal level of PEEPi. In our study, only three patients were intubated because of an acute exacerbation of a COPD. Furthermore, because we always used some level of PEEP in all patients, we think that PEEPi, even if present in some patients, would not have reached a level to substantially influence the results in a clinically significant manner. On the other hand, our results cannot be generalized to patients suspected to have a high basal level of PEEPi. Although we had a low proportion of patients ventilated for an acute exacerbation of COPD, it should be noted that this low proportion is consistent with the most recent international studies on the epidemiology of mechanical ventilation (19). Without additional data, however, our algorithm should be used cautiously in these patients. Finally, we calculated the PTP_{mus} by assuming a triangular shape of the muscle pressure trajectory over time (Equation 2). Direct measurement of the PTP_{mus} using a double-balloon catheter would have yielded a more robust validation of our results, but measuring $P_{mus,Peak}$ and PTP_{mus} in a clinical study would not have been feasible. Because previous physiological studies (24, 25) demonstrated a good correlation between the P_{mus} calculated from PAV variables and the P_{mus} measured with an esophageal catheter, we decided to rely on these data to build our clinical algorithm.

CONCLUSIONS

This study shows that setting PAV+ to achieve a predefined target range of reasonable respiratory effort is feasible, simple, and often sufficient to ventilate patients safely until ventilator withdrawal and extubation. Further studies are needed to investigate whether such an approach could provide benefits beyond current practice.

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SUPPLEMENTAL DIGITAL CONTENT

Bedside adjustment of proportional assist ventilation to target a predefined range of respiratory effort

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Patients and Methods

This was a prospective multicenter observational study involving five university hospitals, four in France (Angers, Créteil, Nice, Rouen) and one in Spain (Barcelona). The study was approved by the Ethics Committee of the Société de Réanimation de Langue Française (French society of intensive care medicine) and the Ethics Committee of Hospital de Sant Pau, Barcelona.

Measurements

The following data were recorded at inclusion under assist-control ventilation (ACV):

- Demographic data: age, gender, height, weight, ICU admission date, intubation date, co-morbidities, mean reason for intubation, SAPS II [1] at ICU admission and at inclusion.
- Hemodynamic data: arterial blood pressure, heart rate, dose of vasopressor (if any).
- Respiratory data: FiO_2, PEEP, inspiratory flow, tidal volume, preset respiratory rate, measured respiratory rate (RR), minute ventilation (V_E), $P_{0.1}$ (average of three consecutive measures).
- Respiratory mechanics: static compliance and resistance of the respiratory system were measured using a tele-inspiratory occlusion.
- Arterial blood gases (ABG).
- RASS score [2], dose of sedative drugs (if any).

During the study, the following parameters were recorded each morning under PAV+:

- Hemodynamic data: arterial blood pressure, heart rate, dose of vasopressor (if any).
- Respiratory data: FiO_2, PEEP, Gain, $P_{mus,Peak}$, expired tidal volume (Vte), insufflation time (Ti), measured respiratory rate (RR), minute ventilation (V_E).
- ABG,

- RASS score, dose of sedative drugs (if any),
- Number of gain adjustments and whether they had been made according to the standard settings or to the additional settings (see below).
- When a weaning trial was performed, its result was reported.

In 45 of the 53 patients, a laptop was connected to the ventilator, using a dedicated software that allowed all the ventilator data to be output every minute throughout the duration of PAV+ ventilation. These data, which were converted into Excel datasets (Microsoft Excel, Microsoft Corporation, Redmond, WA) for subsequent analysis, included: FiO_2, PEEP, Gain, peak airway pressure ($P_{aw,Peak}$), mean airway pressure ($P_{aw,Mean}$), respiratory rate (RR), expired tidal volume (Vte), insufflation time (Ti).

Gain adjustment during PAV+

A Puritan-Bennett 840 ventilator (Covidien, Galway, Ireland) was used to deliver PAV+. The protocol to adjust the gain was designed to maintain the patient within a normal range of respiratory effort. The respiratory muscles pressure-time product (PTP_{mus}) is a reliable measure of respiratory effort [3]. A PTP_{mus} of between 50 and 150 $cmH_2O.s.min^{-1}$ can be considered as a reasonable and acceptable effort during assisted mechanical ventilation [3-4]. However, as the PTP_{mus} was not measurable at the bedside, we used its major component, the peak muscle pressure ($P_{mus,Peak}$), as a surrogate. In fact, in PAV+, it is possible to calculate the $P_{mus,Peak}$ at the bedside. PAV+ uses the equation of motion of the respiratory system to work [5]. During assisted mechanical ventilation, this equation can be written as follows:

$$P_{tot(t)} = P_{aw(t)} + P_{mus(t)} = P_0 + R \times V'_{(t)} + E \times V_{(t)} \qquad \text{[Equation S1]}$$

Where $P_{tot(t)}$: total pressure, $P_{aw(t)}$: airway pressure, $P_{mus(t)}$: muscle pressure, P_0 : starting pressure (corresponding to the total PEEP), R: resistance of the respiratory system, E: elastance of the respiratory system, $V'_{(t)}$: instantaneous flow, $V_{(t)}$: instantaneous volume. During PAV+, the resistance and elastance of the respiratory system are regularly measured by means of tele-inspiratory micro-occlusions [6-7], while the instantaneous flow and volume are continuously monitored. The assistance delivered by the ventilator is then in proportion to this instantaneous flow, volume and respiratory load. Hence, during PAV+, the total pressure needed to inflate the respiratory system is known, and only a proportionality factor – the gain – needs to be set by the clinician.

$$P_{aw(t)} = Gain \times P_{tot(t)} \qquad \text{[Equation S2]}$$

The gain represents the percentage of the total pressure that is assumed by the ventilator, the remaining pressure being assumed by the patient's respiratory muscles. By simply combining equations S1 and S2, we obtain the relation between $P_{aw(t)}$ and $P_{mus(t)}$ in PAV+, showing how the assistance is in proportion to the muscle pressure:

$$P_{aw(t)} - PEEP = P_{mus(t)} \times \frac{Gain}{100-Gain} \qquad \text{[Equation S3]}$$

Given the equation S3, it is possible to calculate the peak muscle pressure ($P_{mus,Peak}$) breath by breath from the values of the PEEP, the gain, and the $P_{aw,Peak}$ pressure, which are continuously monitored on the ventilator screen:

$$P_{mus,Peak} = \left(P_{aw,Peak} - PEEP\right) \times \frac{100-Gain}{Gain} \qquad \text{[Equation S4]}$$

The target range of $P_{mus,Peak}$ was based on the following reasoning: by assuming that the muscle pressure waveform has a triangular shape, and that the end of the inspiratory effort is at the peak muscle pressure, then the PTP_{mus} , which is the area under the muscle pressure curve during the inspiration, can be calculated over a minute (in $cmH_2O.s.min^{-1}$) as follows (**Fig 2**):

$$PTP_{mus} = \frac{P_{mus,Peak} \times Ti}{2} \times RR \qquad \text{[Equation S5]}$$

Where Ti is the inspiratory time and RR the respiratory rate.

Based on this equation, we considered that with usual Ti and RR values, a $P_{mus,Peak}$ between 5 and 10 cmH_2O should allow the PTP_{mus} to remain between 50 and 150 $cmH_2O.s.min^{-1}$. We therefore designed a protocol to adjust assistance during PAV+ that first aimed to keep the $P_{mus,Peak}$ between 5 and 10 cmH_2O.

Consequently, the protocol for setting the ventilator and especially adjusting the gain in PAV+ has been designed as follows:

1. **Initiation of PAV+ ventilation:**

- ***Alarms settings:***

- Airway pressure alarm: 40 cmH_2O
- Respiratory rate alarm: 40 cycles/ minute
- Maximum expired tidal volume: 10 ml/kg of predicted body weight
- Minimum expired tidal volume: 0 ml/kg
- Maximum minute ventilation alarm: 20 l/min
- Minimum minute ventilation alarm : 7 l/min

- ***Ventilatory parameters settings :***

- FiO_2 and PEEP were adjusted according to the standard practice in each participating center.
- Gain: 50%
- Inspiratory trigger: 1 l/min

After starting PAV+ ventilation, the gain was immediately adjusted from the 50% starting gain according to the instructions below. The $P_{mus,Peak}$ was then estimated at least every 8 hours and the gain was adjusted if needed.

2. Algorithm to adjust the gain:

A. P_{mus}-settings:

P_{mus}-settings were based on the measure of $P_{mus,Peak}$ at the bedside, using the grid designed for this purpose (**Fig 1**). In case of a high breath-by-breath variability, the value of the $P_{mus,Peak}$ was obtained by averaging five consecutive measures of the $P_{mus,Peak}$. The aim of the P_{mus}-settings was to adjust the gain to target the $P_{mus,Peak}$ range (between 5 and 10 cmH_2O).

- If $P_{mus,Peak} < 5$ cmH_2O: decrease the gain in steps of 10% until the $P_{mus,Peak}$ exceeds 5 cmH_2O.
- If $P_{mus,Peak} > 10$ cmH_2O: increase the gain in steps of 10% until the $P_{mus,Peak}$ decreases to below 10 cmH_2O.
- If 5 $cmH_2O \leq P_{mus,Peak} \leq 10$ cmH_2O: the $P_{mus,Peak}$ target range is reached, do not modify the gain.

B. Additional settings:

Additional settings had to be used if any of the following appeared despite a $P_{mus,Peak}$ within the target range:

- In case of clinical signs of respiratory distress (RR > 40/min, use of accessory respiratory muscles, dyspnea expressed by an awake patient) lasting for more than 5 min, and/or
- A Vte < 5 ml/kg of predicted body weight, and/or
- The diagnosis of a respiratory acidosis on the ABG:
    - Reassess first the FiO_2 and the PEEP. If they are considered optimal:
    - Increase the gain in steps of 10% until the disappearance of the above signs.
- In case of Vte > 10 ml/kg of predicted body weight, and/or
- The appearance of a respiratory alkalosis on the AGB:

- Look for and treat any other cause of hyperventilation that can generate over-assistance (such as pain, anxiety or metabolic acidosis). If no other cause is found:
- Decrease the gain in steps of 10% until the above signs disappear.

3. Ventilatory criteria that mandate a switch to ACV mode:

Independently of the clinical condition, the PAV+ had to be switched to ACV if it was needed to increase:

- The gain above 85%, and/or
- The FiO_2 above 70%, and/or
- The PEEP above 10 cmH_2O.

4. Weaning from mechanical ventilation:

All patients underwent a daily screening to identify whether they were ready for a weaning trial. The criteria for this trial were:

- The disease causing the need for intubation was controlled
- No clinical sign of respiratory failure
- $FiO_2 \leq 50\%$ and PEEP ≤ 5 cmH_2O
- $SaO_2 \geq 90\%$
- RASS score ≥ -2, without continuous sedation (analgesics permitted)
- Hemodynamic stability without vasopressor

The weaning trial consisted of 1 hour of pressure support ventilation with a pressure support level at 7 cmH_2O and no PEEP.

Extubation required all of the following conditions:

- $SpO_2 \geq 90\%$ with a $FiO_2 \leq 50\%$
- RR ≤ 35/min
- Adequate response to simple commands

- Acceptable cough capacity
- No need for frequent suctioning
- Hemodynamic stability without vasopressor
- No worsening on the ABG if performed (not mandatory)

Quality control

All the investigators reviewed and approved the case report form before the first patient was included, thus ensuring a strict and homogenous method of data collection. Before the start of this study, medical teams at all participating centers received the same specific training in the protocol. This training was based on a specially designed tool to adjust the gain during PAV+. This tool consisted of a slideshow specifically developed for this purpose. During the study, telephone assistance from the coordinating center (Henri Mondor Hospital) was available 24h/d. The collected data were entered into a database (Microsoft Excel; Microsoft Corporation, Redmond, WA) and then reviewed for inconsistencies and data entry errors by one investigator (GC).

Statistics

Statistical analyses were performed with Statistical Package for the Social Sciences (version 16.0, SPSS, Chicago, IL, USA). Continuous data are expressed as the median (25^{th}, 75^{th} percentile). Continuous data were compared before and after the start of PAV+ ventilation using a Wilcoxon signed-rank test. Comparisons between patients that were or were not extubated at the end of the PAV+ ventilation were made using a Mann-Whitney U test. A two-sided p-value of 0.05 or less was considered statistically significant.

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Article 2 :

Comparaison d'une titration de l'assistance en NAVA et en VSAI basée sur l'analyse des indices d'effort respiratoire

Comparison between neurally adjusted ventilatory assist and pressure support ventilation levels in terms of respiratory effort

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Key words:

Neurally adjusted ventilatory assist; Pressure support ventilation; Respiration, Artificial; Ventilator Weaning; Respiratory muscles; Assisted mechanical ventilation.

ABSTRACT

Objectives To understand the potential equivalence between neurally adjusted ventilatory assist (NAVA) and pressure support (PS) ventilation levels in terms of respiratory muscle unloading. To compare the respiratory pattern, variability, synchronization, and neuro-muscular coupling within comparable ranges of assistance.

Design Prospective single-center physiological study.

Setting A 13-bed university medical intensive care unit.

Patients Eleven patients recovering from respiratory failure.

Interventions The following levels of assistance were consecutively applied in a random order: NAVA levels 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7 $cmH_2O.\mu volt^{-1}$; PS levels: 7, 10, 15, 20, 25 cmH_2O.

Measurements Flow, airway pressure, esophageal pressures, and peak EAdi were continuously recorded. Breathing effort was calculated. To express the % of assist assumed by the ventilator, the total pressure including muscular and ventilator pressure was calculated.

Main Results The median % of assist ranged from 33 [24-47] % to 82 [72-90] % between PS 7 and 25 cmH_2O. Similar levels of unloading were observed for NAVA levels from 0.5 (46 [40-51] %) to 2.5 (80 [74-84] %) $cmH_2O.\mu volt^{-1}$. Tidal variability was higher during NAVA and ineffective efforts appeared only in PS. In NAVA, double triggering occurred sometimes when EAdi signal depicted a biphasic aspect and an abnormal oscillatory pattern was frequently observed from 4 $cmH_2O.\mu volt^{-1}$. For both modes, the relationship between peak EAdi and muscle pressure depicted a curvilinear profile.

Conclusions In patients recovering from acute respiratory failure, levels of NAVA between 0.5 and 2.5 $cmH_2O.\mu volt^{-1}$ are comparable to PS levels ranging from 7 to 25 cmH_2O in terms of respiratory muscle unloading. NAVA provides better patient ventilator interactions but can be sometimes excessively sensitive to EAdi in terms of triggering.

INTRODUCTION

Neurally adjusted ventilatory assist (NAVA) is a partial ventilatory support mode that delivers inspiratory airway pressure (Paw) in proportion to the electrical activity of the diaphragm (EAdi) (1), which is obtained by the mean of an esophageal catheter containing an electrode array in front of the crural diaphragm. The magnitude of the instantaneous Paw is thus determined by the value of the instantaneous EAdi multiplied by a proportionality factor (NAVA level, in cm $H_2O.\mu volt^{-1}$) set by the clinician. The EAdi signal is correlated to the transdiaphragmatic pressure (2). NAVA therefore delivers its assistance in proportion to the patient's inspiratory effort. Physiological studies have consistently reported that NAVA improves patient-ventilator interactions as compared to pressure support ventilation (PSV) during both invasive and noninvasive ventilation (3-11). Adjusting the NAVA level remains however a matter of uncertainty. In fact, as NAVA is a proportional ventilatory mode, modifying the NAVA level usually alters the respiratory effort often without markedly changing the respiratory pattern (4, 6, 10, 12-14), making difficult to set NAVA on usual parameters like respiratory rate or tidal volume. Furthermore, the neuro-muscular coupling, meaning the proportionality factor between electrical activity and actual respiratory effort has been reported to be different among patients (15). It is therefore difficult to determine the level of respiratory effort from the EAdi value in clinical practice. Nowadays PSV remains the most frequently used ventilatory mode for partial support ventilation (16), and clinicians are thus familiar with the routine clinical appreciation of the effects of various levels of pressure support. Information provided by measured respiratory efforts indices values over a wide range of NAVA levels and their comparison with a wide range of PS levels would therefore have meaningful implications for clinicians wishing to use NAVA and for future research in this field.

In this study, we aimed at detecting the potential correlations between NAVA and PS levels in terms of muscle unloading in patients recovering from acute respiratory failure. We additionally compared the respiratory pattern, variability, synchronization, and neuro-muscular coupling within comparable ranges of assistance in terms of respiratory effort.

MATERIALS AND METHODS

This was a prospective single-center physiological study. An extensive description of the study protocol is provided in the Supplemental Digital Content.

Patients

Eleven patients were included in the Henri Mondor university hospital medical ICU, Créteil, France. The protocol was approved by the ethics committee CPP-Ile-de-France VIII (number: 2008-A00859-46), and written informed consent was obtained from every patient or their next of kin. Patients recovering from an acute respiratory failure who satisfied the following inclusion criteria were considered eligible: ability to trigger every ventilatory cycle, RASS(17) $\geq$ -3, $SpO_2 \geq 90\%$ with $FiO_2 \leq 60\%$ and positive end expiratory pressure (PEEP) $\leq$ 8 cm H_2O, temperature between 36 and 39°C. Patients were not included in case of any contraindication to esophageal catheter insertion, severe cardiac arrhythmia with heart rate > 130/min, epinephrine or norepinephrine infusion > 0.3 µg/kg/min, age below 18 y-o, pregnancy, or moribund patient. All patients were included within the 36 hours after fulfilling the inclusion criteria. No patient received any sedative drug during the study.

Study protocol

Every patient was studied in semi-recumbent position. After inclusion patients were connected to a Servo-i ventilator integrating the NAVA module (Maquet Critical Care, Solna, Sweden) and a modified EAdi catheter with esophageal balloon (Neurovent, Toronto, ON, Canada) was positioned as recommended (18). We used a dedicated tool implemented into the

ventilator to guide the correct positioning of the EAdi catheter at the nearest centimeter (18). Both catheter position and EAdi signal stability were regularly checked using this tool throughout the protocol. During NAVA, the instantaneous value of the airway pressure delivered by the ventilator is a direct amplification of the EAdi signal, using the following equation:

$$Paw_t = EAdi_t \times NAVA\ level$$

where Paw_t is the instantaneous airway pressure (in cm H_2O), $EAdi_t$ the instantaneous EAdi signal value (in μvolt) recorded by the EAdi catheter, and the NAVA level (in cm $H_2O.\mu volt^{-1}$) as set by the clinician. The EAdi catheter used in our study allowed recording of both the EAdi signal and the esophageal pressure signal by the mean of an additional esophageal balloon mounted on the catheter. As the catheter position was determined by the EAdi signal, the position of the esophageal balloon might sometimes slightly vary from its ideal location (19). We therefore calculated the ratio between esophageal and airway pressure during an occlusion maneuver. When its value was below 0.8 (five patients), it was used as a correction factor to recalculate the respiratory effort indices.

The protocol consisted of ventilating patients using the PEEP initially set by the clinician: 1) in NAVA using nine different NAVA levels in a random order (0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7 cm $H_2O.\mu volt^{-1}$); 2) in PSV using five different PS levels in a random order (7, 10, 15, 20, 25 cm H_2O). Because the breathing pattern usually reaches its steady-state rapidly (20), each level of assistance was applied for 5 to 10 minutes in order to analyze synchrony and respiratory parameters at the new steady state.

Measurements

Flow, airway and esophageal pressures, and EAdi were continuously recorded throughout the study protocol (Fig.1) and stored in a laptop for subsequent analysis, as described in the Supplemental Digital Content. The 20 last consecutives recorded cycles at

each level of assistance were used to analyze muscle unloading indices and respiratory pattern, as well as their coefficient of variation (computed as the ratio of the standard deviation to the mean, expressed as a percentage). The last three recorded minutes of each level of assistance were used to analyze patient-ventilator synchronization and to compute asynchrony index, using the esophageal pressure signal to characterize asynchronies as previously described (21, 22). The esophageal pressure waveform allowed identifying every inspiratory effort and therefore to compute both the patient's respiratory rate (defined as every inspiratory effort per minute) and the ventilator's respiratory rate (defined as every triggered cycle per minute).

Indices of muscle unloading

The muscle pressure was computed as the difference between esophageal pressure and the chest wall elastic recoil curve, which was calculated as the volume divided by the theoretical chest wall compliance (4% of the predicted value for the vital capacity per cm H_2O (23)), assuming that no patient had abnormal chest wall compliance. The peak muscle pressure represented the muscle pressure calculated at the nadir of esophageal pressure value during the inspiratory effort. The esophageal pressure time product (PTPes) was computed as previously described (24, 25). To express the percentage of assistance in a comparable way between the two modes we calculated the following ratio: $\frac{(Pawpeak-PEEP)}{(Pawpeak-PEEP)+Pmuspeak} . 100$ (26). It represented the proportion of the total pressure (ventilator and muscular pressure) that was assumed by the ventilator, the remaining percentage representing the part of the total pressure that was generated by the respiratory muscles. Neuro-muscular coupling was assessed through the relationship between $EAdi_{peak}$ and $Pmus_{peak}$.

The 20 last consecutive recorded cycles at each level of assistance were used to analyze muscles unloading indices and the respiratory pattern, as well as their coefficient of variation.

Statistics

Statistical analyses were performed with Statistical Package for the Social Sciences (version 16.0, SPSS Inc, Chicago, IL). Continuous data are expressed as the median (25^{th}-75^{th} percentile). The effect of the level of assistance during NAVA and PSV was assessed separately by a Friedman test, then a Wilcoxon test with Benjamini-Hochberg correction for paired measures. Two-sided P values less than 0.05 were considered significant.

RESULTS

Every patient completed the study. In one patient however, the value of the esophageal pressure signal was not reliable enough and 10 patients remained for analysis of indices of muscle unloading derived from esophageal pressure. Furthermore, increasing the NAVA level above 4 cm $H_2O.\mu volt^{-1}$ frequently led to an abnormal hyper-variable pattern, as described below, making it not feasible to appropriately analyze respiratory variables. We therefore report data of the NAVA titration between 0.5 and 4 cm $H_2O.\mu volt^{-1}$. Main patient's demographic and clinical characteristics at inclusion are reported in Table 1. Four patients had underlying chronic heart failure and one had underlying asthma. At the time of inclusion, three patients had unilateral and six bilateral infiltrates on the chest X-ray, three patients also had bilateral small pleural effusion. No patient had a suspicion of increased intra-abdominal pressure. Additional results are provided in the Supplemental Digital Content.

Muscle unloading

Respiratory effort indices decreased when increasing the level of assistance during both NAVA and PSV titrations (Fig. 2, see Table E1 and E2 in the Supplemental Digital Content for numerical values). At NAVA level 0.5 cm $H_2O.\mu volt^{-1}$, grouped values (Fig. 2) as well as individual values (Supplemental Digital Content Fig. E1) of $EAdi_{peak}$, $Pmus_{peak}$, and PTPes were close to those observed at PS 7 cm H_2O. The percentage of assistance was

however slightly higher during NAVA 0.5 cm $H_2O.\mu volt^{-1}$ than during PS 7 cm H_2O, and was up to 80% from NAVA level 2.5 cm $H_2O.\mu volt^{-1}$ (Fig. 2). From NAVA level 2.5 cm $H_2O.\mu volt^{-1}$, grouped (Fig. 2) and individual values (Supplemental Digital Content Fig. E1) of respiratory muscle unloading indices were comparable from those observed in PS 25 cm H_2O. Levels of NAVA between 0.5 and 2.5 cm$H_2O.\mu volt^{-1}$ appeared therefore comparable to pressure support levels ranging from 7 to 25 cm H_2O in terms of respiratory muscle unloading. At NAVA level 1.5 cm $H_2O.\mu volt^{-1}$, the respiratory muscle unloading indices values were close to those observed at PS 15 cm H_2O.

Respiratory pattern

During both NAVA and PSV titrations, the peak airway pressure (Paw_{peak}) increased with increasing level of assistance (Fig. 3, see Fig. E2 in the Supplemental Digital Content for individual values). From NAVA level 2.5 cm $H_2O.\mu volt^{-1}$, half of the patients exhibited a Paw_{peak} over 30 cm H_2O. At NAVA level 0.5 cm $H_2O.\mu volt^{-1}$ the tidal volume (Vt) was significantly different than the Vt observed at other NAVA levels. From NAVA level 1 cm $H_2O.\mu volt^{-1}$, there was no further significant difference in the Vt over the NAVA titration. Individual analysis however showed that two patients exhibited a continuous increase in the Vt over the NAVA titration (Supplemental Digital Content Fig. E2). During PSV, the increase in the assistance was significantly associated with an increase in Vt from PS 15 cm H_2O. During both NAVA and PSV titration the V_E did not significantly vary.

Variability

Over the NAVA titration, the coefficient of variation of Vt was closest to the coefficient of variation of $EAdi_{peak}$ than during the PSV titration (Supplemental Digital Content: Tables E1 and E2, and Fig. E3). Increasing the NAVA level above 4 cm $H_2O.\mu volt^{-1}$ however frequently led to an abnormal hyper-variable pattern suggesting an oscillatory phenomenon (Fig.4). .

Synchronization

Double triggering occurred during NAVA, usually with a low incidence whatever the level of assistance: one patient exhibited an asynchrony index above 10% at three NAVA levels (Supplemental Digital Content: Table E1 and Fig. E4). During PSV, ineffective efforts occurred when increasing the level of assistance: the asynchrony index ranged from 0.0 % (0.0-0.0) at PS 7 cm H_2O to 0.0 % (0.0-30.1) at PS 25 cm H_2O (Supplemental Digital Content: Table E2 and Fig. E4).

Neuro-muscular coupling

The relationship between $EAdi_{peak}$ and $Pmus_{peak}$ was not linear over the titrations of both NAVA and PSV but curvilinear, following an exponential shape (Fig. 5). Therefore, the neuro-muscular coupling depended on the level of assistance: at low levels of assistance, the proportionality factor between EAdi and actual respiratory effort, even though variable among patients, was higher than at high levels of assistance.

DISCUSSION

To our knowledge, this study is the first to compare respiratory effort indices during titration of assistance in both NAVA and PSV. The main findings of our study are the followings: 1) pressure support levels ranging from 7 to 25 cm H_2O were comparable to levels of NAVA between 0.5 and 2.5 $cmH_2O.\mu volt^{-1}$ in terms of respiratory muscle unloading. Within these two ranges: 2) the respiratory pattern was comparable between the two modes; 3) the respiratory drive variability was equivalent but translated into less variability of tidal volume in PSV than in NAVA; 4) above NAVA level 4 $cmH_2O.\mu volt^{-1}$ hyper-variable respiratory pattern suggesting oscillatory phenomenon frequently occurred. 5) the relationship between electrical activity of the diaphragm and actual respiratory effort depicted a curvilinear profile depending on the level of assistance.

Muscle unloading

It has been previously described that EAdi as well as respiratory muscle unloading indices decreased while the NAVA level increased (6, 12). The comparison of such indices over wide titrations of both NAVA and PSV is original in our study. It allowed comparing the same window of respiratory muscles unloading with the two titrations, one being made with a widely used ventilatory mode now familiar to most clinicians (16). During NAVA, most of the reduction of the respiratory muscles unloading indices occurred between NAVA level 0.5 and 2.5 cm $H_2O.\mu volt^{-1}$. At NAVA 0.5 cm $H_2O.\mu volt^{-1}$ half of the patients exhibited relatively high but still acceptable PTPes values (meaning less than 200 cm $H_2O.s.min^{-1}$, which represents the maximal value reported by Jubran and Tobin in patients tolerating a weaning trial (24)). In normal subjects breathing spontaneously, the PTPes has been reported to be 86 ± 21 $cmH_2O \cdot s \cdot min^{-1}$ (27), which was obtained here with a NAVA level around 1.5 cm $H_2O.\mu volt^{-1}$. From NAVA level 2.5 cm $H_2O.\mu volt^{-1}$, the assistance delivered by the ventilator was at least as high as the one delivered with PSV 25 cm H_2O, with only little changes between 2.5 and 4.0 cm $H_2O.\mu volt^{-1}$. In our patients recovering from acute respiratory failure, NAVA levels between 0.5 and 2.5 $cmH_2O.\mu volt^{-1}$ appeared therefore comparable to PS ranging from 7 to 25 cm H_2O in terms of respiratory muscles unloading.

Respiratory pattern

The respiratory pattern observed during both NAVA and PSV titrations is consistent with what was reported by Patroniti et al. (6). Contrary to other reports (12, 28) however, we did not observe a steep increase in the airway pressure at the onset of the titration followed by a plateau phase, at least in the majority of our patients. Brander et al. described this two-phase response using a prototype system in which NAVA levels were expressed in different unit (12). Passat et al claimed they used this two-phase response to set the NAVA level by doing an increase in the assistance by 0.1 cm $H_2O.\mu volt^{-1}$ every 20 seconds (28), which represents a

different method of titration. In our study the minimal NAVA level (0.5 cm $H_2O.\mu volt^{-1}$) already resulted in a substantial level of support. One may therefore speculate that an initial steep increase in airway pressure would have been observed if the titration had started without any NAVA assistance.

Variability

NAVA is supposed to reproduce the variability of the neural respiratory drive (1) . During both PSV and NAVA, the variability of the $EAdi_{peak}$ was preserved. The variability of the Vt was, however, less representative of the respiratory drive variability than during NAVA. This finding is consistent with previous report from Schmidt et al. (29). As previously reported (6, 29), we observed a stable variability of $EAdi_{peak}$ over the first part of the NAVA titration, followed by a substantial increase from NAVA level 3. We further found that from NAVA level 4 cm $H_2O.\mu volt^{-1}$ a hyper-variable pattern that clearly represents a sign of over-assistance during NAVA (6, 12) frequently occured.

Synchronization

Our data about patient-ventilator asynchrony validated previous observations. We especially reported the occurrence of double triggering during NAVA in some patients, independently of the NAVA level. This asynchrony was the consequence of alterations of the EAdi signal leading to a biphasic aspect, as described by Piquilloud et al. (8). We also observed an increase in the incidence of ineffective efforts with the increase in the assistance during PSV, which is consistent with previous reports (6, 8, 10, 11, 22, 30) and is attributed to overassistance, leading to passive insufflation of large tidal volumes (see Fig. 1) and subsequent dynamic hyper-inflation (8, 11, 30). This explains the increasing difference observed between RRv and RRp over the PSV titration.

Neuro-muscular coupling

We found that the relationship between $EAdi_{peak}$ and $Pmus_{peak}$ was curvilinear over both the NAVA and PSV titrations, meaning that the proportionality factor between EAdi and actual respiratory effort depends on the level of assistance. Contrary to our findings, Bellani et al reported that the proportionality factor between $EAdi_{peak}$ and $Pmus_{peak}$, even though different between patients, remained stable at different levels of assistance (15). This observation was not reproduced on a breath by breath basis in a recent report from Akoumianaki et al (31). Furthermore, the range of assistance tested in the Bellani study was narrow compared to our study (0.5, 1 and 1.5 cm $H_2O.\mu volt^{-1}$). Lastly, the stability of the neuro-muscular coupling for a given level of assistance over the time is unknown and should be addressed in further study.

Clinical implications

Our findings have meaningful clinical implications. In fact, despite many physiological reports NAVA has not yet been translated into daily clinical practice especially because the adjustment of the NAVA level remains a matter of concern. One of the reasons is that clinicians have no clue about the meaning of the electrical levels and gain, or more practically, how to set it.

Brander et al. described a two-phase evolution in airway pressure over a NAVA titration: a steep increase at the onset of the titration, and then a less rapid increase (12). Authors proposed to set the NAVA level at the onset of the second phase. Observing such a two-phase response may need at least some training and other teams including us, were unable to retrieve it (6). Furthermore, this approach needs at least ten to 15 minutes (28), which is not realistic in the clinical settings. As NAVA is a proportional ventilatory mode, changing the NAVA level has usually a minor impact on Vt and RR over a certain range, and mainly alters the respiratory effort as shown in our study and in previous reports (4, 6, 10, 12-14). It would make sense to adjust the NAVA level in order to target a desirable range of

respiratory effort as it has been shown to be feasible in another proportional ventilatory mode (26). As discussed above however, we found that the proportionality coefficient that linked the respiratory muscle pressure and the EAdi was not stable over a wide range of NAVA levels but followed a curvilinear shape depending on the level of assistance. This makes therefore difficult to assess the actual respiratory effort during NAVA without having some pragmatic points of reference. Because PSV has now become one of the most frequently used mode of mechanical ventilation in the ICU (16), we therefore thought that giving the clinicians some correspondence about the effects of given PS and NAVA levels in terms of respiratory muscle unloading could help with the clinical implementation of this technique and future research in the field. Clinicians may draw pragmatic information from the correspondence of levels of assistance between NAVA and PSV over both titrations in terms of respiratory muscle unloading. Especially our data suggest that in most patients the NAVA level can be kept $\leq$ 2.5 cm $H_2O.\mu volt^{-1}$. It is important to stress that two out of our eleven patients had a tidal volume above 10 and even 15 ml/kg of ideal body weight while in a proper muscle unloading range in NAVA (see Supplemental Digital Content Fig. E3).

Limitations

We studied a limited sample of patients heterogeneous in terms of age, severity, length of mechanical ventilation and ventilatory demand. Our results may therefore not apply to all patients receiving assisted mechanical ventilation, although they appear remarkably consistent across all patients. Our patients however recovered from various medical and surgical etiologies of acute respiratory failure and exhibited relatively homogeneous responses to both titrations. Second, the calculation of the respiratory muscles indices needed applying a correction factor when the ratio between esophageal and airway pressure was below 0.8 during the occlusion maneuver (19). This was due to the fact that the position of the esophageal balloon was determined by the proper position of the electrode array for the

recording of the EAdi as both devices were on the same catheter. It was therefore not possible to re-adjust the position of the esophageal balloon (32). We cannot exclude that the application of this correction factor influenced the inter-individual heterogeneity and therefore the absolute value of our results. As our main aim was however to compare respiratory effort indices at varying levels of PSV and NAVA in the same patients, this correction factor was not likely to significantly influence the meaning of our results.

CONCLUSIONS

In our study, levels of NAVA between 0.5 and 2.5 cm $H_2O.\mu volt^{-1}$ were comparable to pressure support levels ranging from 7 to 25 cm H_2O in terms of respiratory muscle unloading. Within these two ranges, the respiratory pattern and neural variability were comparable between the two modes but the variability of the resulting tidal volume better reflected the variability of the respiratory drive during NAVA as compared to PSV. Above NAVA level 3 cm $H_2O.\mu volt^{-1}$ the percentage of assistance exceeded 80% and from NAVA level 4 cm $H_2O.\mu volt^{-1}$ the overall variability frequently reached an abnormal oscillatory pattern. As the relationship between EAdi and respiratory effort values followed a curvilinear shape depending on the level of assistance, it is not feasible to calculate at the bedside the % assist in clinical routine. Such pragmatic points of reference are therefore crucial for clinicians wishing using NAVA in the clinical settings and for future research in this field.

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FIGURE LEGENDS

Figure 1

Representative recordings of Flow, airway pressure (Paw, esophageal pressure (Pes), and electrical activity of the diaphragm (EADI) over one breath at pressure support level 7 cm H_2O (PS 7) and 25 cm H_2O (PS 25), NAVA level 0.5 cm $H_2O.\mu volt^{-1}$ (NAVA 0.5) and 2.5 cm $H_2O.\mu volt^{-1}$ (NAVA 2.5). At high levels of assistance, note that contrary to NAVA most of the insufflation occurred passively during PSV.

Figure 2

Representation of the median (diamond) and interquartile range of the peak of electrical activity of the diaphragm ($EADI_{peak}$), the peak muscle pressure ($Pmus_{peak}$), the esophageal pressure time product (PTPes), and the percentage of assistance (%assist) during both the titration of NAVA and pressure support ventilation. Dotted grey lines underline values observed at highest and lowest pressure support levels. * $p < .05$ versus the lowest level of assistance within the same ventilatory mode; † $p < .05$ versus the highest level of assistance within the same ventilatory mode.

Figure 3

Representation of the median (diamond) and interquartile range of the peak airway pressure (Paw_{peak}), ventilator respiratory rate (RRv), tidal volume (Vt), and minute ventilation (V_E) during both the titration of NAVA and pressure support ventilation. Dotted grey lines underline values observed at highest and lowest pressure support levels. * $p < .05$ versus the lowest level of assistance within the same ventilatory mode; † $p < .05$ versus the highest level of assistance within the same ventilatory mode.

Figure 4

Representative recording of the hyper-variable respiratory pattern that frequently occurred when increasing the level of assistance during NAVA. Paw: airway pressure, Pes: esophageal pressure, EADI: electrical activity of the diaphragm.

Figure 5

Relationship between peak muscle pressure of the respiratory muscles ($Pmus_{peak}$) and peak electrical activity of the diaphragm ($EADI_{peak}$) at different levels of assistance in neurally adjusted ventilatory assist (NAVA) and pressure support ventilation (PSV). Each black circle represents the mean (with error bars) values at one level of assistance. The lowest level of assistance of each titration is on the right part of each graph ($N_{0.5}$: NAVA level 0.5 cm $H_2O.\mu volt^{-1}$; PS_7: pressure support level 7 cm H_2O), and the highest on the left (N_4: NAVA level 4 cm $H_2O.\mu volt^{-1}$; PS_{25}: pressure support level 25 cm H_2O).

Table 1 Demographic and clinical characteristics at inclusion

Sex	Age (Yrs.)	Height (cm)	Weight (kg)	Diagnosis	SAPS II	Days from intubation	RASS	PSl (cm H_20)	FiO_2	PEEP (cm H_20)	$Pa0_2/FiO_2$ (mm Hg)	Duration of mechanical ventilation	ICU Outcome
M	69	182	74	ARDS – Legionella pneumonia	42	21	-2	16	0.3	5	294	35	Surv
M	37	160	49	ARDS – Aspiration pneumonia	25	12	0	12	0.3	5	272	13	Surv
M	75	160	87	ARDS – TRALI	96	3	-2	ACV	0.5	8	175	8	Surv
F	84	167	82	ARDS – MRSA pneumonia and septic shock	47	5	0	ACV	0.4	5	270	8	Surv
F	57	154	57	CPE	79	4	+1	12	0.3	8	457	5	Surv
M	81	168	110	ARDS – MSSA endocarditis and mediastinitis	53	6	0	10	0.6	5	180	39	Surv
F	68	165	83	ARDS – pulmonary aspergillosis	47	6	-3	14	0.4	8	225	11	Non Surv
F	64	160	61	ARDS – pneumocystis pneumonia	32	11	0	12	0.3	5	377	12	Surv
F	82	160	67	ARDS – fecal peritonitis with septic shock	61	11	0	20	0.4	7	172	19	Surv
M	69	165	55	ARDS – post renal transplantation peritonitis	49	6	0	12	0.6	5	172	12	Surv
F	82	162	76	CPE post mitral valve replacement	45	11	0	12	0.3	5	287	15	Surv

Definitions of abbreviations: SAPS II: Simplified Acute Physiology Score(31); RASS: Richmond Agitation Sedation Scale(16); PSl: Pressure Support level; PEEP: Positive end expiratory pressure; ARDS: Acute respiratory distress syndrome; TRALI: Transfusion related acute lung injury; MRSA: Methicillin resistant Staphylococcus aureus; MSSA Methicillin sensitive Staphylococcus aureus; CPE: cardiogenic pulmonary edema; ACV: assist control ventilation; Surv: survivor; Non surv: non survivor.

Figure 1

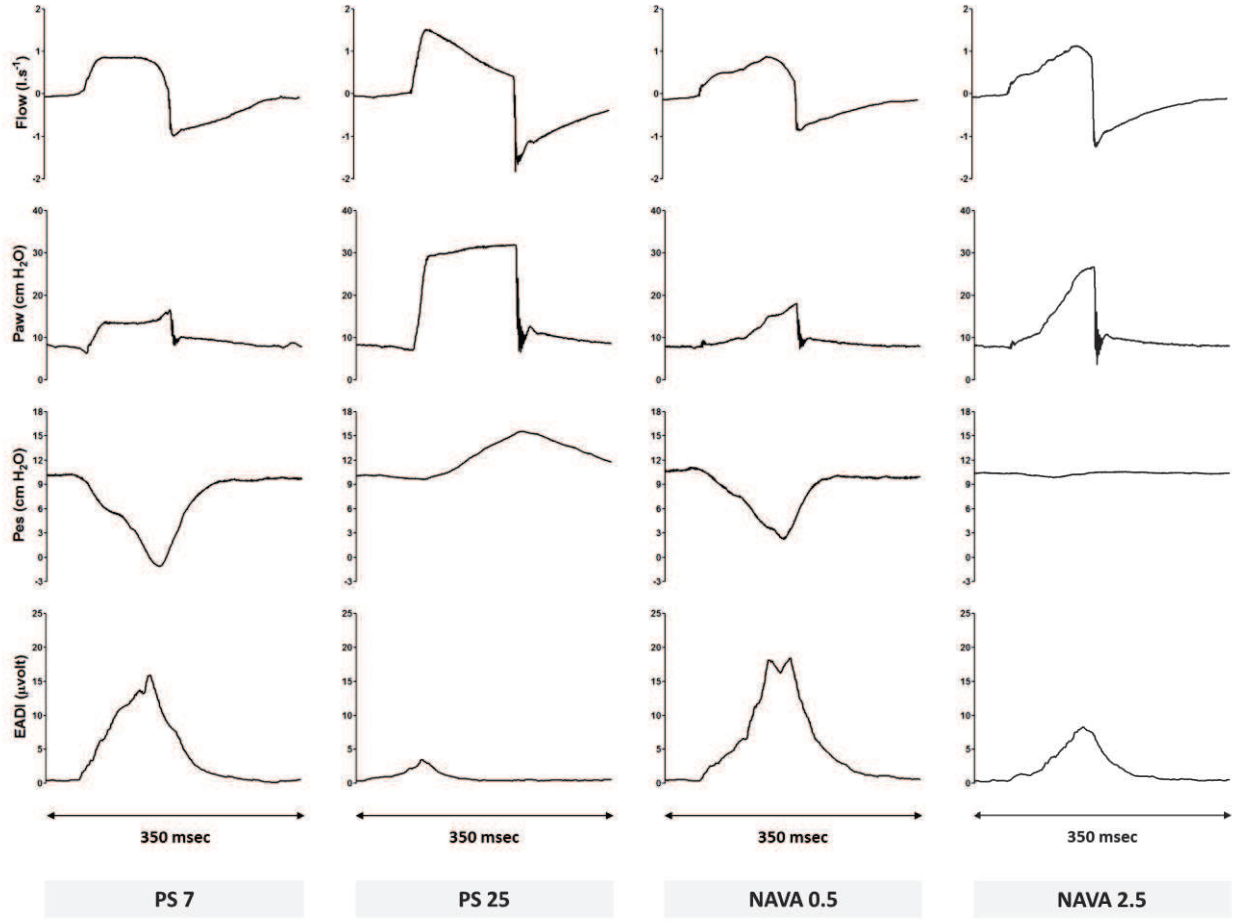

Flow (l.s-1)
Paw (cm H2O)
Pes (cm H2O)
EADi (µvolt)
350 msec
350 msec
350 msec
350 msec
PS 7
PS 25
NAVA 0.5
NAVA 2.5

Figure 2

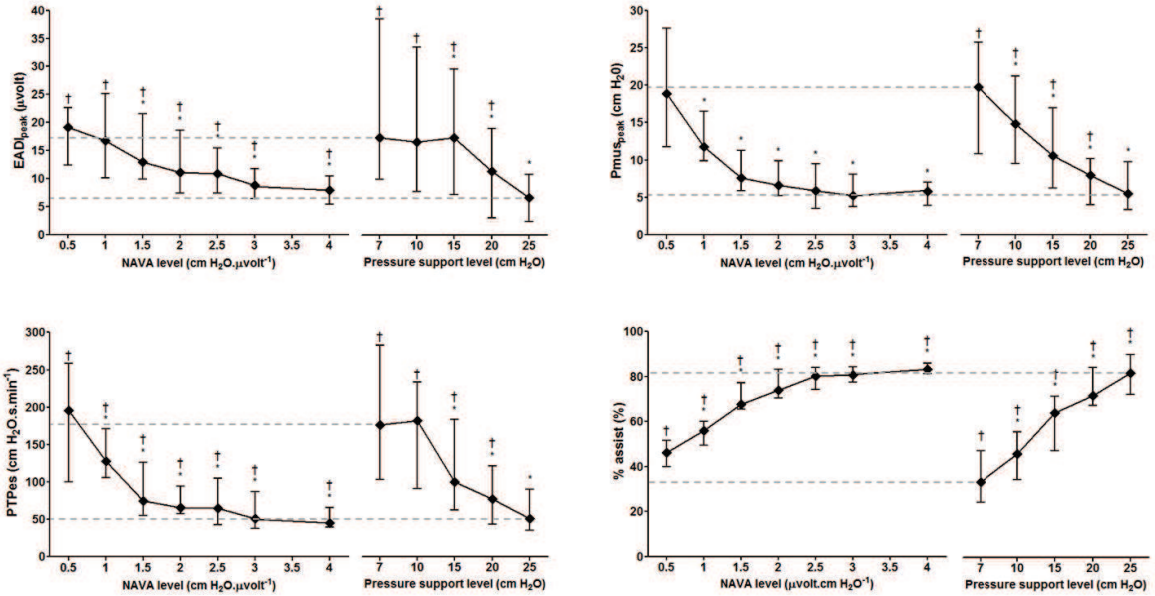

EAD$_{peak}$ (µvolt)
Pmus$_{peak}$ (cm H$_2$0)
PTPes (cm H$_2$O.s.min^{-1})
% assist (%)
NAVA level (cm H$_2$O.µvolt^{-1})
Pressure support level (cm H$_2$O)
NAVA level (µvolt.cm H$_2$O^{-1})

Figure 3

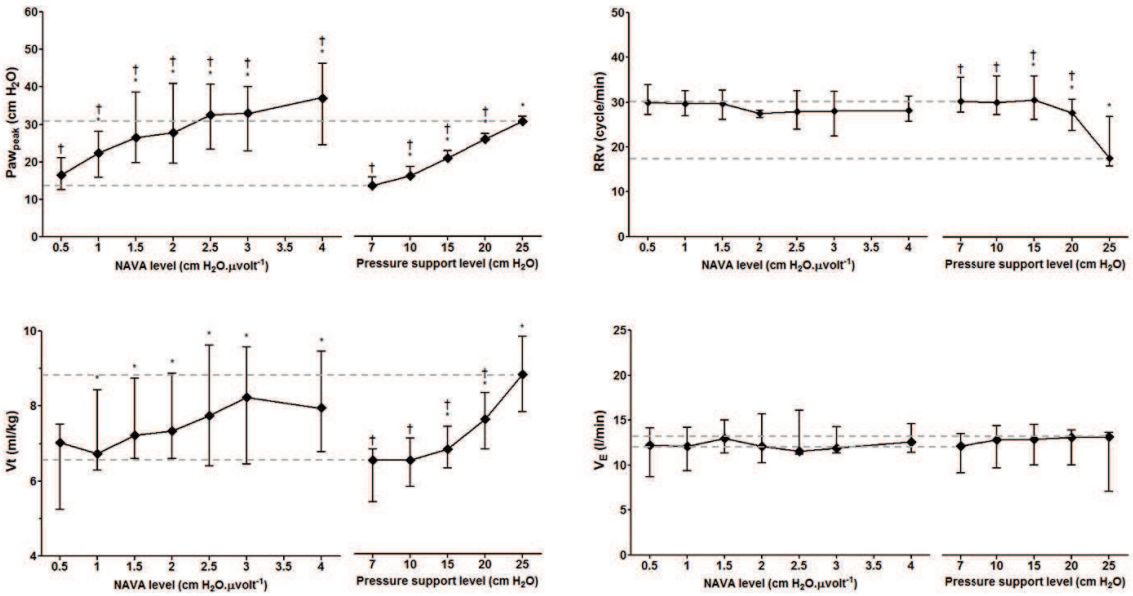

Paw$_{peak}$ (cm H$_2$O)
RRv (cycle/min)
Vt (ml/kg)
V$_E$ (l/min)
NAVA level (cm H$_2$O.µvolt^{-1})
Pressure support level (cm H$_2$O)

Figure 4

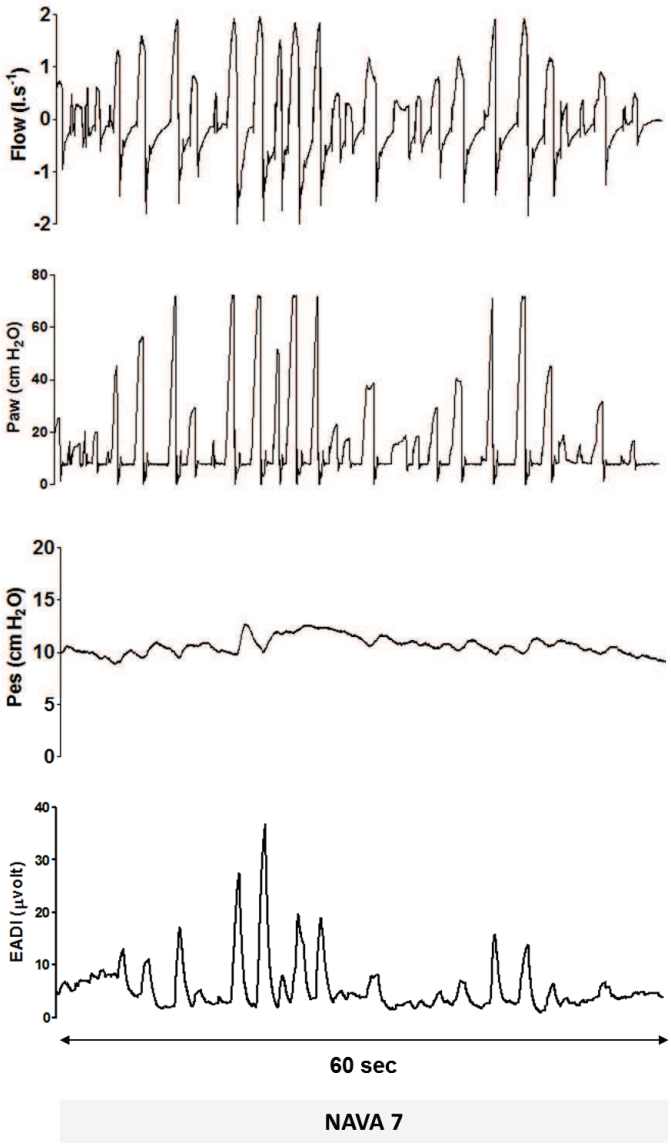
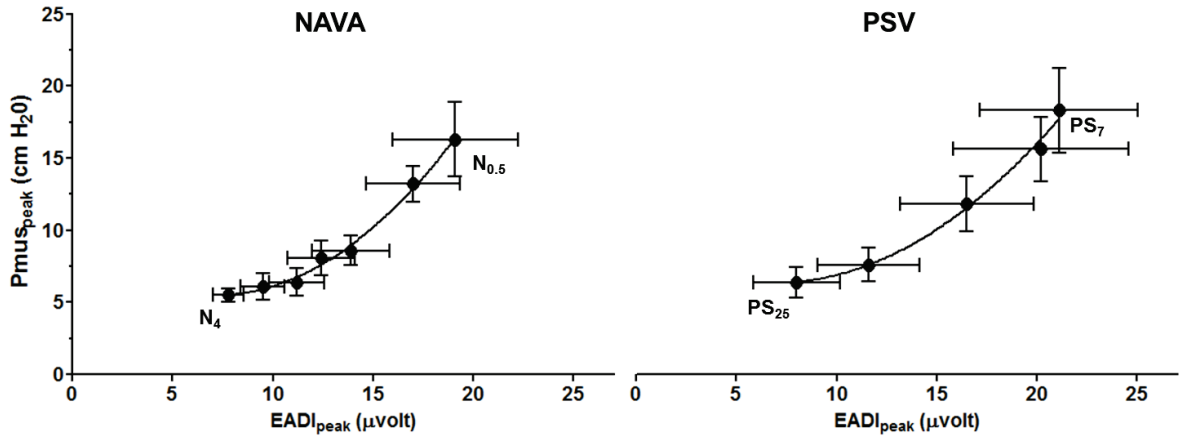

Flow (l.s-1)
2
1
0
-1
-2
Paw (cm H2O)
80
60
40
20
0
Pes (cm H2O)
20
15
10
5
0
EADI (µvolt)
40
30
20
10
0
60 sec
NAVA 7

Figure 5


NAVA
PSV
Pmus$_{peak}$ (cm H$_2$0)
EADI$_{peak}$ (μvolt)
EADI$_{peak}$ (μvolt)
N$_4$
N$_{0.5}$
PS$_{25}$
PS$_7$
0
5
10
15
20
25

Supplemental Digital Content

Comparison between neurally adjusted ventilatory assist and pressure support ventilation levels in terms of respiratory effort

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METHODS

Additional description of the study protocol

The study was conducted between January 2009 and May 2011.
As soon as they were included, patients were connected to a Servo-I ventilator integrating the NAVA module (Maquet Critical Care, Solna, Sweden). The adapted EAdi catheter (Neurovent, Toronto, ON, Canada) was then positioned as recommended (1). Patients were first ventilated in NAVA with NAVA level set at 1 cm $H_2O.\mu volt^{-1}$ to ensure that the catheter signal was stable and the tolerance to the mode acceptable. They were suctioned and positioned in a semi recumbent position. The same heat and moisture exchanger was used in all patients. The FiO_2 was maintained at level set clinically before the study.
If the patient was stable under these conditions, the protocol started:

1) Ventilation in NAVA:
- The inspiratory neural trigger was set at 0.5 cm $H_2O.\mu volt^{-1}$ and the inspiratory flow trigger was set at 1 L/min.
- The following NAVA levels were randomly applied while using the PEEP set clinically before the study: 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 7 cm $H_2O.\mu volt^{-1}$.

2) Ventilation in PSV:
- The inspiratory trigger was set at the lowest possible value without the occurrence of auto-triggering.
- The expiratory trigger was set at 25% of the peak inspiratory flow.
- The following PSL were randomly applied while using the PEEP set clinically before the study: 7, 10, 15, 20, and 25 cm H_2O.

Each level of assistance was applied for 5 to 10 minutes in order to reach a steady state.

Measurements: additional details and definitions

Flow was measured with a non-heated pneumotachograph (Fleish No. 2, Lausanne, Switzerland) inserted between the endotracheal tube and the Y-piece of the circuit and connected to a differential pressure transducer (Validyne MP45, ± 2 cm H_2O, Northridge, CA, USA). Volume was obtained by integration of the flow signal. Airway pressure was measured with a differential pressure transducer (Validyne MP45, ± 70 cm H_2O, Northridge, CA, USA) placed between the endotracheal tube and the pneumotachograph. Esophageal pressure was measured, using balloons mounted on the esophageal catheter, with differential pressure transducers (Validyne MP45, ± 70 cm H_2O, Northridge, CA, USA). Their positions were verified as previously described (2, 3). The position of the esophageal balloon however was determined by the proper position of the electrode array for the recording of the EAdi as both devices were on the same catheter. When the ratio between esophageal and airway pressure was below 0.8 during the occlusion maneuver, this ratio was used as a correction factor for the calculation of the esophageal pressure time product and the muscle pressure. Signals were acquired online over the whole study protocol, one file being created at each level of assistance, using an analog-digital converter (MP 100; Biopac systems, Goleta, CA, USA) sampled at 200 Hz, and stored in a laptop computer for subsequent analysis with the Acqknowledge 3.7.3 software (Biopac systems, Goleta, CA, USA). Electrical activity of the diaphragm (EAdi) signal was recorded using the dedicated software NAVA Tracker 2.0 (Maquet Critical Care, Solna, Sweden) which recorded cycle-by-cycle values of EAdi peak ($EADI_{peak}$) and EADI mean ($EADI_{mean}$).

Respiratory pattern

The followings parameters were analyzed from the above recordings:

- Insufflation time (Ti): Time from the onset to the end of positive flow,
- Coefficient of variation of Ti (CV-Ti),
- Expiratory time (Te): time from the onset to the end of negative flow,
- Coefficient of variation of Te (CV-Te)
- Peak airway pressure (Paw_{peak})
- Coefficient of variation of Paw_{peak} (CV-Paw_{peak})
- Mean airway pressure (Paw_{mean})

- Patient's neural respiratory rate (RRp): every inspiratory effort identified on the esophageal pressure waveform per minute,
- Ventilator respiratory rate (RRv): every triggered cycle per minute
- Minute ventilation (V_E),
- Tidal volume (Vt)
- Coefficient of variation of Vt (CV-Vt)

Muscle unloading indices definitions

The muscle pressure was computed as the difference between esophageal pressure and the chest wall elastic recoil curve, which was calculated as the volume divided by the chest wall compliance. Measuring chest wall compliance using esophageal pressure however requires performing a passive controlled insufflation, which was not feasible in our patients breathing spontaneously. We therefore used theoretical value of the chest wall compliance (4% of the predicted value for the vital capacity per cm H_2O (4)).

The peak muscle pressure represented the muscle pressure calculated at the nadir of esophageal pressure value during the inspiratory effort. The esophageal pressure time product (PTPes) was computed as previously described (5). The percentage of assistance was computed as follows: $\frac{(Pawpeak-PEEP)}{(Pawpeak-PEEP)+Pmuspeak} . 100$ (6). It represented the proportion of the total pressure that was assumed by the ventilator, the remaining percentage representing the part of the total pressure that was generated by the respiratory muscles.

The 20 last consecutive recorded cycles at each level of assistance were used to analyze the respiratory pattern and muscles unloading indices, as well as their coefficient of variation. The EAdi signals being recorded with another software than the other collected signals, it was not possible to reliably match the peak of EAdi ($EAdi_{peak}$) with the peak muscle pressures ($Pmus_{peak}$) on a breath-by-breath basis.

Asynchrony

Major patient-ventilator asynchronies were defined and detected by one investigator (GC) by visual inspection of the three last minutes of each recording as previously published using the esophageal pressure and the EAdi as indicating the real patient's activity (7). Especially, ineffective effort was defined by the presence of an inspiratory effort detected on the esophageal pressure waveform not followed by an assisted cycle; double-triggering was defined as two cycles separated by a very short time during the same inspiratory effort. A

global asynchrony index (AI) was computed as previously reported (7, 8), defined as the total number of the asynchrony events divided by the total number of triggered and non-triggered ventilator cycles: AI (%) = [number of events / (ineffective triggerings + ventilator cycles)] x 100.

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ADDITIONAL TABLES

Table E1 Muscles unloading, respiratory pattern, variability and synchronization at different NAVA levels

	Neurally Adjusted Ventilatory Assist						
NAVA level (cm $H_2O.\mu volt^{-1}$)	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**
Muscle unloading							
$EAdi_{peak}$ (μvolt)	19.2 [12.4-22.6] †	16.8 [10.1-25.1] †	12.9 [9.9-21.5] *†	11.1 [7.4-18.6] *†	10.9 [7.4-15.4] *†	8.8 [6.4-11.7] *†	7.9 [5.4-10.4] *†
PTPes ($cm\ H_2O.s.min^{-1}$)	196 [100-259] †	128 [106-171] *†	74 [55-126] *†	65 [57-95] *†	65 [43-105] *†	51 [38-87] *†	45 [39-66] *†
$Pmus_{peak}$ ($cm\ H_2O$)	18.9 [11.8-27.6]	11.8 [9.8-16.5] *	7.6 [5.8-11.3] *	6.6 [5.2-9.8] *	5.9 [3.5-9.4] *	5.2 [3.7-8.0] *	5.8 [3.9-7.0] *
% assist (%)	46 [40-51] †	56 [49-60] *†	68 [66-77] *†	74 [70-83] *†	80 [74-84] *†	81 [77-84] *†	83 [81-86] *†
Respiratory pattern							
Paw_{peak} (cmH_20)	16.5 [12.7-21.2] †	22.5 [15.9-28.2] *†	26.5 [20.4-36.6] *†	27.9 [20.9-40.9] *†	32.5 [23.4-40.7] *†	33.1 [22.9-40.0] *†	36.9 [25.7-46.3] *†
Paw_{mean} (cmH_2O)	7.7 [6.5-9.8]	8.5 [7.3-10.4] *	10.0 [8.4-13.0] *	10.5 [8.7-12.6] *	11.0 [9.2-13.5] *	11.2 [9.3-12.1] *	11.1 [9.2-12.5] *
Ti (sec)	0.8 [0.7-1.0] ‡	0.7 [0.7-0.9]	0.7 [0.7-0.9]	0.8 [0.7-0.9]	0.8 [0.7-0.9]	0.8 [0.6-1.0]	0.7 [0.6-0.8]
Te (sec)	1.1 [1.1-1.4]	1.3 [1.1-1.4]	1.4 [1.1-1.5]	1.4 [1.3-1.6]*	1.5 [1.1-1.7] *§	1.5 [1.2-1.7]	1.5 [1.2-1.7] *
Ti/Ttot (%)	40 [33-44] †	35 [33-40] *†	37 [29-40] †	34 [32-39] *†	36 [31-39] *†	35 [27-38] *†	32 [30-35] *†
RRv (cycle/min)	30.0 [27.5-33.9]	29.6 [27.0-32.5]	27.5 [26.1-32.7]	27.3 [25.5-28.2]	27.0 [24-32.5]	27.5 [22.4-32.4]	27.1 [25.7-31.3]
RRp (br/min)	30.0 [28.3-32.5]	28.2 [26.3-32.4]	27.0 [26.1-31.1]	27.0 [25.7-28.0]	25.6 [23.9-27.3]	27.1 [22.9-29.4]	25.4 [22.5-26.7]
Vt (ml/kg)	7.0 [5.2-7.5]	6.7 [6.3-8.4] *	7.2 [6.6-8.7] *	7.3 [6.6-8.9] *	7.8 [6.4-9.6] *	8.2 [6.4-9.6] *	8.0 [6.8-9.5] *
RR/Vt (br/min/l)	89 [58-104]	77 [57-88]*	74 [45-80]*	68 [45-74] *	65 [43-89]*	64 [36-76] *	71 [37-75]*
V_E (l/min)	12.2 [8.7-14.1]	12.1 [9.4-14.2]	13.0 [10.3-15.0]	12.1 [10.3-15.7]	11.5 [10.6-16.1]	11.9 [10.7-14.3]	12.6 [11.0-14.6]
Variability							
CV-$EAdi_{peak}$ (%)	21.5 [18.6-40.7]	18.6 [14.5-37.1]	22.8 [16.1-30.0] †	17.8 [14.4-35.6] †	20.1 [15.0-27.1] †	19.7 [16.5-35.1] †	35.5 [18.8-38.2]
CV-Paw_{peak} (%)	12.6 [8.6-13.8] †‡	15.6 [9.5-19.1] †	13.4 [11.5-17.4] †	12.7 [11.0-27.1] †	14.4 [12.5-20.3] *†§	14.5 [12.6-20.6] *†	21.5 [14.2-26.1] *
CV-Vt (%)	10.9 [8.0-21.5] †	12.4 [10.4-16.0]	14.5 [11.5-21.9]	17.1 [8.9-24.8]	18.2 [12.5-31.5] §	16.7 [9.5-27.3]	23.6 [12.5-26.8]*
CV-Ti (%)	10.1 [6.0-16.8]†	9.3 [7.9-11.5] †	9.0 [7.6-15.1] †	11.1 [8.4-13.5] †	12.3 [9.2-16.8]	11.2 [8.9-17.5] †	17.1 [9.4-18.7]
CV-Te (%)	12.4 [6.6-19.5]	16.8 [9.6-20.6]	11.5 [7.4-15.2]	17.7 [8.2-22.7]	14.5 [7.7-21.7]	21.8 [9.1-24.8]	20.4 [10.1-23.6]
Synchronization							
Asynchrony index (%)	0.0 [0.0-1.8]	0.0 [0.0-5.1]	0.0 [0.0-2.8]	0.0 [0.0-0.7]	0.0 [0.0-1.6]	0.0 [0.0-0.9]	0.0 [0.0-0.9]

Definitions of abbreviations: $EAdi_{peak}$: peak electrical activity of the diaphragm; PTPes : esophageal pressure time product; $Pmus_{peak}$: peak muscle pressure; % assist: percentage of assistance (computed as: $\frac{(Pawpeak-PEEP)}{(Pawpeak-PEEP)+Pmuspeak} . 100$); Paw_{peak} : peak airway pressure; Paw_{mean} : mean airway pressure ; Ti : insufflation time ; Te : expiratory time ; RRv: ventilator respiratory rate; RRp: patient's neural respiratory rate; Vt: tidal volume; V_E: minute ventilation; CV-$EAdi_{peak}$: coefficient of variation of $EAdi_{peak}$; CV-Paw_{peak}: coefficient of variation of Paw_{peak}; CV-Vt: coefficient of variation of Vt; CV-Ti: coefficient of variation of Ti; CV-Te: coefficient of variation of Te.

* $p < 0.05$ vs lowest level of assistance, † $p < 0.05$ vs highest level of assistance, ‡ $p < 0.05$ between NAVA level 0.5 cm $H_2O.\mu volt^{-1}$ and PS 7 cm H_2O, § $p < 0.05$ between NAVA level 2.5 cm $H_2O.\mu volt^{-1}$ and PS 25 cm H_2O.

Table E2 Muscles unloading, respiratory pattern, variability and synchronization at different pressure support levels

	Pressure support ventilation				
Pressure support level (cmH_20)	**7**	**10**	**15**	**20**	**25**
Muscle unloading					
$EAdi_{peak}$ (µvolt)	17.3 [9.9-38.5] †	16.6 [7.8-33.5] †	17.3 [7.2-29.5] *†	11.4 [3.1-19.0] *†	6.7 [2.4-10.8] *
PTPes ($cm\ H_2O.s.min^{-1}$)	176 [103-282] †	182 [91-233] †	100 [63-183] *†	77 [43-121] *†	51 [35-90] *
$Pmus_{peak}$ ($cm\ H_2O$)	19.7 [10.8-25.6] †	14.8 [9.5-21.1] *†	10.5 [6.2-16.9] *†	7.9[4.0-10.1] *†	5.5 [3.3-9.7] *
% assist (%)	33 [2624-47] †	46 [35-56] *†	64 [47-72] *†	72 [68-85] *†	82 [72-90] *
Respiratory pattern					
Paw_{peak} (cmH_20)	13.6 [13.3-16.0] †	16.2 [15.9-18.7] *†	21.0 [20.6-22.9] *†	26 [24.8-27.5] *†	30.8 [29.4-32.1] *
Paw_{mean} (cmH_2O)	7.6 [7.1-9.3] †	8.6 [7.9-10.0] *†	10.2 [9.2-11.3] *†	11.4 [10.4-12.2] *†	12.4 [10.8-14.1] *
Ti (sec)	0.7 [0.6-0.9] †‡	0.7 [0.6-0.8] †	0.7 [0.6-0.9] †	0.7 [0.7-1.0]	0.9 [0.7-1.1]
Te (sec)	1.2 [1.0-1.5] †	1.2 [0.9-1.5] †	1.3 [1.1-1.4] †	1.5 [1.2-2.0]* †	2.3 [1.3-2.9] *§
Ti/Ttot (%)	38 [30-42] †	37 [29-41] †	36 [31-41] †	36 [29-39] †	32 [25-34]
RRv (cycle/min)	30 [27-35] †	30 [27-35] †	30 [26-35] *†	27 [19-30] *†	17 [16-26] *
RRp (br/min)	30 [28-34] †	30 [27-36] †	31 [26-34] †	28 [23-34] †	26 [24-27]
Vt (ml/kg)	6.5 [5.4-6.8] †	6.5 [5.8-7.0] †	6.8 [6.3-7.4] *†	7.6 [6.8-8.3] *†	8.8 [7.8-9.8] *
RR/Vt (br/min/l)	96 [62-105] †	80 [55-90] †	78 [53-101] *†	64 [42-77] *†	41 [28-53] *
VE (l/min)	12.1 [9.1-13.5]	12.8 [9.7-14.3]	12.9 [10.0-14.5]	13.1 [10.0-13.9]	13.2 [8.5-13.6]
Variability					
$CV\text{-}EAdi_{peak}$ (%)	18.9 [15.2-24.9]	19.0 [15.5-28.8]	20.6 [14.7-21.9]	27.1 [14.6-29.8]	24.2 [19.2-47.6]
$CV\text{-}Paw_{peak}$ (%)	1.3 [0.8-1.9] ‡	1.0 [1.0-1.4]	0.9 [0.7-1.4]	0.9 [0.6-2.0]	0.7 [0.4-1.8] §
CV-Vt (%)	8.6 [4.5-15.6]	8.4 [4.1-12.9]	6.4 [4.0-8.7]	3.6 [2.9-7.0]	5.4 [3.0-9.9] §
CV-Ti (%)	6.6 [3.7-15.2]	6.7 [4.1-10.5]	6.2 [3.7-9.3]	4.4 [3.9-10.6]	5.4 [4.9-10.5]
CV-Te (%)	11.8 [8.3-17.3]	12.9 [8.9-17.3]	11.0 [6.5-14.0]	15.0 [5.7-34.4]	23.0 [6.7-42.7]
Synchronization					
Asynchrony index (%)	0.0 [0.0-0.0]	0.0 [0.0-0.7]	0.0 [0.0-1.6]	0.0 [0.0-11.9]	0.0 [0.0-30.1]

Definitions of abbreviations: $EAdi_{peak}$: peak electrical activity of the diaphragm; PTPes : esophageal pressure time product; $Pmus_{peak}$: peak muscle pressure; % assist: percentage of assistance (computed as: $\frac{(Pawpeak-PEEP)}{(Pawpeak-PEEP)+Pmuspeak} . 100$); Paw_{peak} : peak airway pressure; Paw_{mean} : mean airway pressure ; Ti : insufflation time ; Te : expiratory time ; RRv: ventilator respiratory rate; RRp: patient's neural respiratory rate; Vt: tidal volume; V_E: minute ventilation; CV-$EAdi_{peak}$: coefficient of variation of $EAdi_{peak}$; CV-Paw_{peak}: coefficient of variation of Paw_{peak}; CV-Vt: coefficient of variation of Vt; CV-Ti: coefficient of variation of Ti; CV-Te: coefficient of variation of Te.

* $p < 0.05$ vs lowest level of assistance, † $p < 0.05$ vs highest level of assistance, ‡ $p < 0.05$ between NAVA level 0.5 cm $H_2O.\mu volt^{-1}$ and PS 7 cm H_2O, § $p < 0.05$ between NAVA level 2.5 cm $H_2O.\mu volt^{-1}$ and PS 25 cm H_2O

ADDITIONAL FIGURES

Figure E1

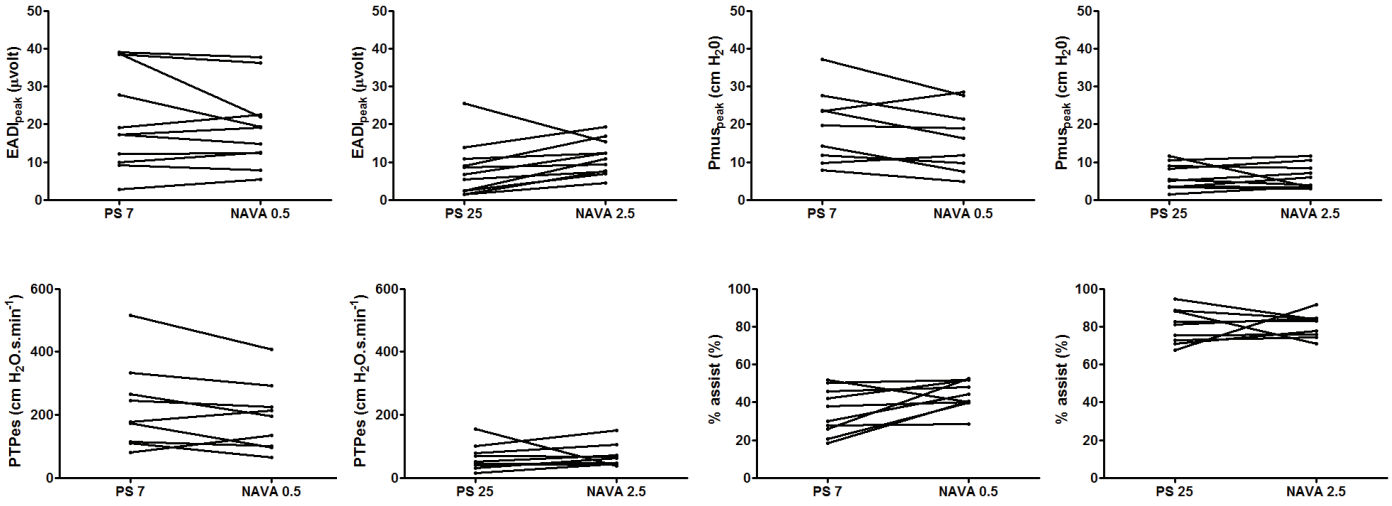

Figure E1. Individual comparisons of $EAdi_{peak}$, $Pmus_{peak}$, PTPes and %assist between PS 7 cm H_2O and NAVA level 0.5 cm $H_2O.\mu volt^{-1}$, and between PS 25 cm H_2O and NAVA level 2.5 cm $H_2O.\mu volt^{-1}$.

Figure E2

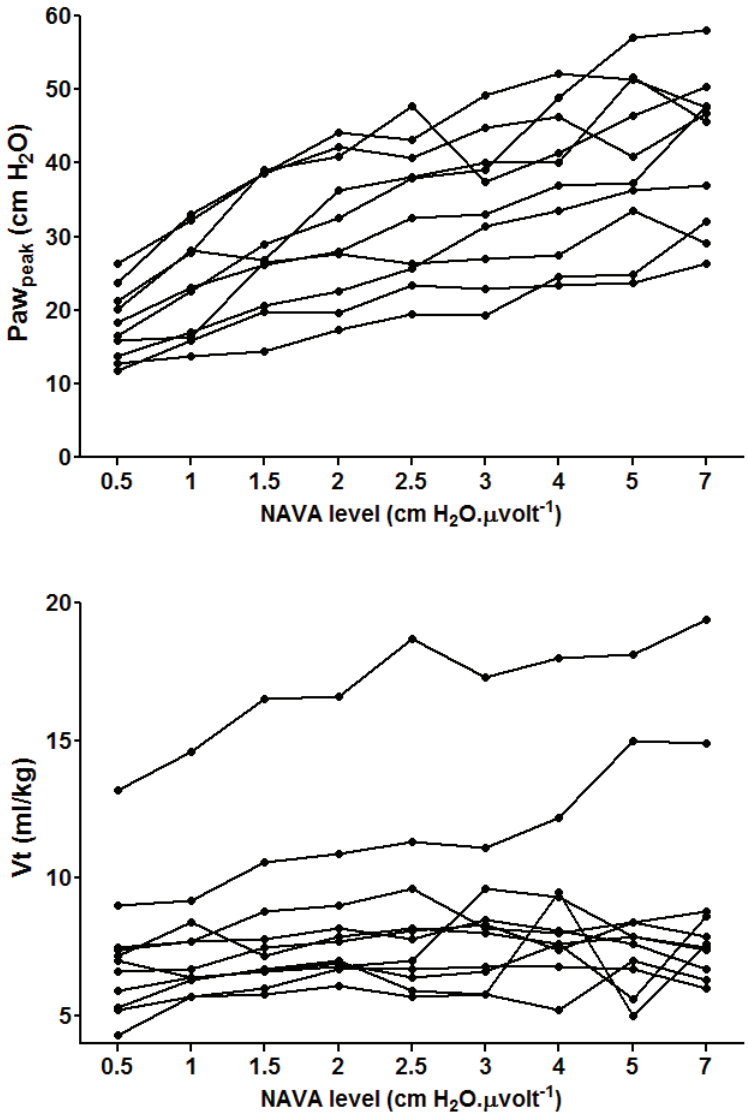

Figure E2. Representation of individual values of peak airway pressure (Paw_{peak}) and tidal volume (Vt) during the titration of NAVA.

Figure E3

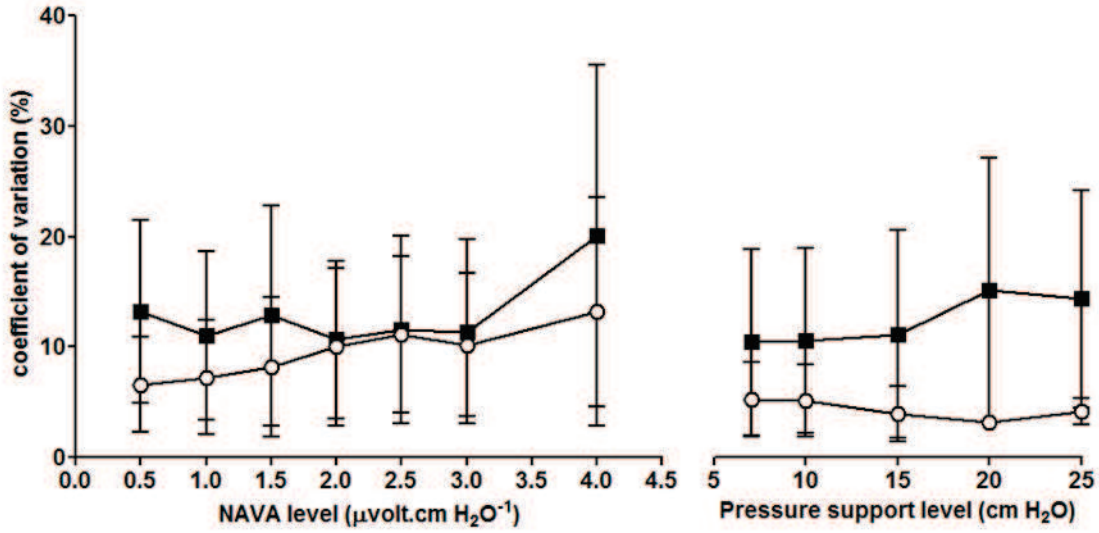

Figure E3

Representation of the coefficient of variation (median and standard error) of the peak electrical activity of the diaphragm (black squares) and the tidal volume (open circles).

Figure E4

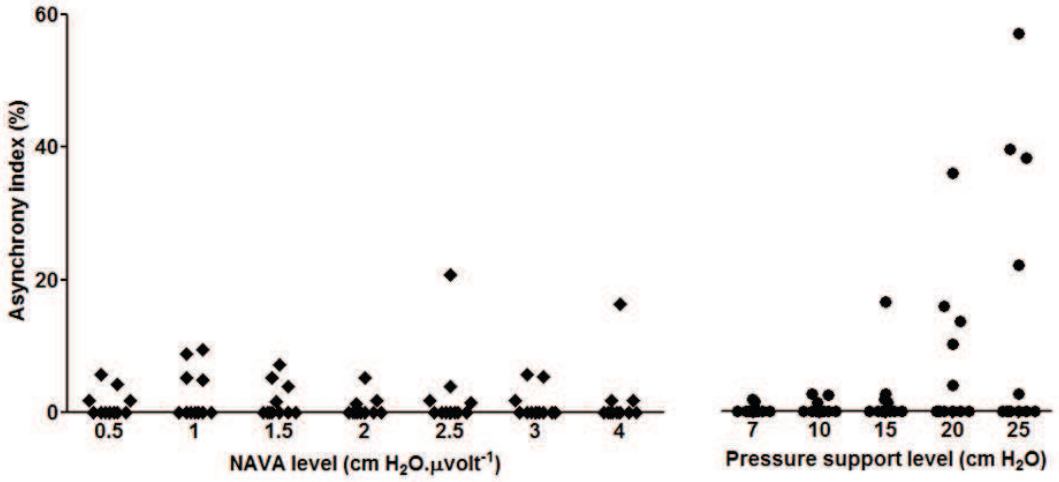

Figure E4

Representation of the individual value of the asynchrony index during both the titrations of NAVA and pressure support ventilation. Black diamonds represent double triggering, black circles represent ineffective effort. Every asynchrony recorded during NAVA was a double triggering, and every asynchrony recorded during pressure support ventilation was an ineffective effort.

Article 3 :

Evaluation clinique de l'incidence des asynchronies patient-ventilateur en VNI avec et sans l'utilisation de l'algorithme VNI sur des ventilateurs variés de réanimation.

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ORIGINAL

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Performance of noninvasive ventilation algorithms on ICU ventilators during pressure support: a clinical study

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Abstract *Objective:* To evaluate the impact of noninvasive ventilation (NIV) algorithms available on intensive care unit ventilators on the incidence of patient-ventilator asynchrony in patients receiving NIV for acute respiratory failure.
Design: Prospective multicenter randomized cross-over study.
Setting: Intensive care units in three university hospitals.
Methods: Patients consecutively admitted to the ICU and treated by NIV with an ICU ventilator were included. Airway pressure, flow and surface diaphragmatic electromyography were recorded continuously during two 30-min periods, with the NIV (NIV+) or without the NIV algorithm (NIV0). Asynchrony events, the asynchrony index (AI) and a specific asynchrony index influenced by leaks (AIleaks) were determined from tracing analysis.
Results: Sixty-five patients were included. With and without the NIV algorithm, respectively, auto-triggering was present in 14 (22%) and 10 (15%) patients, ineffective breaths in 15 (23%) and 5 (8%) ($p = 0.004$), late cycling in 11 (17%) and 5 (8%) ($p = 0.003$), premature cycling in 22 (34%) and 21 (32%), and double triggering in 3 (5%) and 6 (9%). The mean number of asynchronies influenced by leaks was significantly reduced by the NIV algorithm ($p < 0.05$). A significant correlation was found between the magnitude of leaks and AIleaks when the NIV algorithm was not activated ($p = 0.03$). The global AI remained unchanged, mainly because on some ventilators with the NIV algorithm premature cycling occurs.
Conclusion: In acute respiratory failure, NIV algorithms provided by ICU ventilators can reduce the incidence of asynchronies because of leaks, thus confirming bench test results, but some of these algorithms can generate premature cycling.

Keywords Noninvasive ventilation · Mechanical ventilation · Patient-ventilator interaction · Asynchrony

Introduction

Non-invasive ventilation (NIV) has become a standard of care in patients with acute respiratory failure [1–3]. Although practices may vary, intensive care unit (ICU) ventilators are often preferred by ICU practitioners to perform NIV during acute respiratory failure [4]. However, a recent study showed that severe patient-ventilator asynchrony is present in 43% of these patients, mainly as a result of leaks at the patient-mask interface [5]. This latter finding is not surprising, as leaks are known to interfere with several key aspects of ventilator function [6–10]. The problem with ICU ventilators is that they were originally designed to function with a leak-free closed circuit, conditions that are very different from the leak-prone conditions of NIV [11]. To address this issue, manufacturers have developed NIV algorithms, so-called "NIV modes" on their machines, whose main function is to alleviate the impact of leaks on ICU ventilator performance [10]. A recent bench model study showed that NIV algorithms could indeed correct this problem, albeit with variations between machines [10]. However, to date no study has shown whether the same results could be achieved in the clinical setting.

The purpose of this study was to evaluate the impact of NIV algorithms on the incidence, nature and severity of patient-ventilator asynchrony in patients receiving NIV for acute respiratory failure.

Materials and methods

This was a prospective, randomized, cross-over study, conducted at three university hospital ICUs, one medical (Creteil), and two medical-surgical (Brussels, Geneva). The protocol was approved by the ethics committee of each participating center. All patients in the ICU receiving NIV for an acute respiratory failure were eligible. Informed consent was obtained from the patients. Patients were included as soon as possible after initiation of NIV. All patients were ventilated with ICU ventilators routinely used in the units and in which bench model tests had shown the efficacy of the NIV algorithm in correcting various asynchrony parameters [10]: Evita 4 and XL (Draeger, Lübeck, Germany), Servo I (Maquet, Solma, Sweeden), G5 (Hamilton Medical, Rhäzuns Switzerland) and Engström Carestation (GE Healthcare, Fairfield, CT). NIV algorithms are based on technology varying from one manufacturer to another [10]. Their goal is to attenuate the impact of leaks on ICU ventilator function by measuring and compensating for leaks while adapting alarms. They are usually referred to as "NIV modes," although they are not ventilatory modes. On our bench test they partly corrected the negative effects of leaks on trigger delay, auto-triggering, pressurization and late cycling [10]. We observed on the bench test that with the correction of late cycling, we had no more ineffective efforts in obstructive respiratory mechanics conditions. Without leaks, the NIV algorithm performs generally as well as pressure support when the NIV algorithm is not activated, except on the Servoi, in which trigger delay is increased by 18% in normal respiratory mechanics from 110 to 130 ms (unpublished data).

Criteria for initiating NIV followed the usual practice guidelines of each center, which are based on previous published studies on hypercapnic [12] and non-hypercapnic respiratory failure [2] (see ESM).

Patients presenting any contraindication to NIV were excluded [13].

NIV was applied via a standard oro-nasal mask, in Pressure Support mode. NIV settings were those made by the clinician in charge of the patient, according to usual standard procedure of each center. No adjustments were made by the investigators, except the activation and deactivation of the NIV algorithm. Two consecutive NIV sessions in random order were applied, one with the NIV algorithm (NIV+), the other without the NIV algorithm (NIV0). The duration of each session was 30 min. When the NIV algorithm was not activated, alarms were silenced when necessary and patients surveyed as usual.

The respiratory parameters [respiratory rate, expired tidal volume (VTE), minute volume, leaks at the mask, inspiratory times of the patient (ti_p) and of the ventilator (ti_v)] were assessed by analysis of the flow, pressure and surface diaphragmatic electromyographic activity (EMGdi) as described in a previous study [5]. Asynchrony events (ineffective triggering, double-triggering, auto-triggering, premature cycling and delayed cycling) were detected by visual inspection of the recordings (Figs. 1, 2). The assessment of respiratory parameters and asynchrony events is detailed in the ESM.

A global asynchrony index (AI) was computed as previously published [5, 14]. An AI > 10% was considered as severe [5, 14]. As a new concept, we defined a specific asynchrony index, which takes into account only asynchronies influenced by leaks (AIleaks). Detailed definitions are provided in the ESM.

Statistics

Statistics were performed with SigmaStat 2.0–SPSS Science (Systat, San Jose, CA) and Stata version IC10 (STATA Corp., College Station, TX).

Continuous data are expressed as median (25th–75th percentile) or mean (SD) depending on the parametric or non-parametric nature of data distribution.

Inter-group comparison of continuous variables was made with a paired Student's *t* test or a Wilcoxon test,

depending on the parametric or non-parametric nature of data distribution. Inter-group comparison of continuous variables for more than two groups were made by a one-way ANOVA test or an ANOVA on ranks depending on the parametric or non-parametric nature of data distribution. To isolate the group or groups that differ from the others, a multiple comparison procedure was used: an Al Pairwise Multiple Comparison Procedure (Dunn's Method). Comparison of the number of patients presenting each type of asynchrony between the two groups was made by a McNemar test.

The relationship between leaks and delta of each type of event described above was explored through linear regression.

To determine which parameters were associated with AIleaks, with or without the NIV algorithm, a generalized estimation equations model (a linear regression model using an exchangeable correlation matrix) and ANCOVA (covariance analysis) were used. Variables that in univariate analysis presented a significance level of 0.10 or less were included in the model. The effect of leaks on AIleaks was then analyzed on the two samples (NIV0 and NIV+).

All p values <0.05 were considered significant.

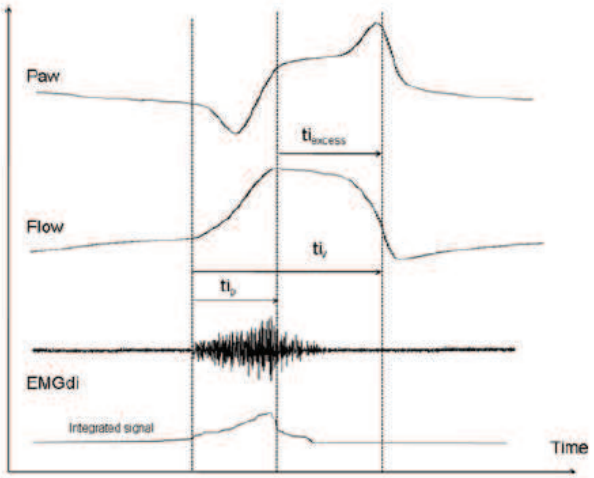

Fig. 1 Pressure-time, flow-time and diaphragmatic EMG-time tracings, allowing determination of patient inspiratory time (ti_p), ventilator inspiratory time (ti_v) and inspiratory time in excess (ti_{excess})

Results

Seventy-five consecutive patients were screened, five of whom refused to participate; 70 patients were therefore

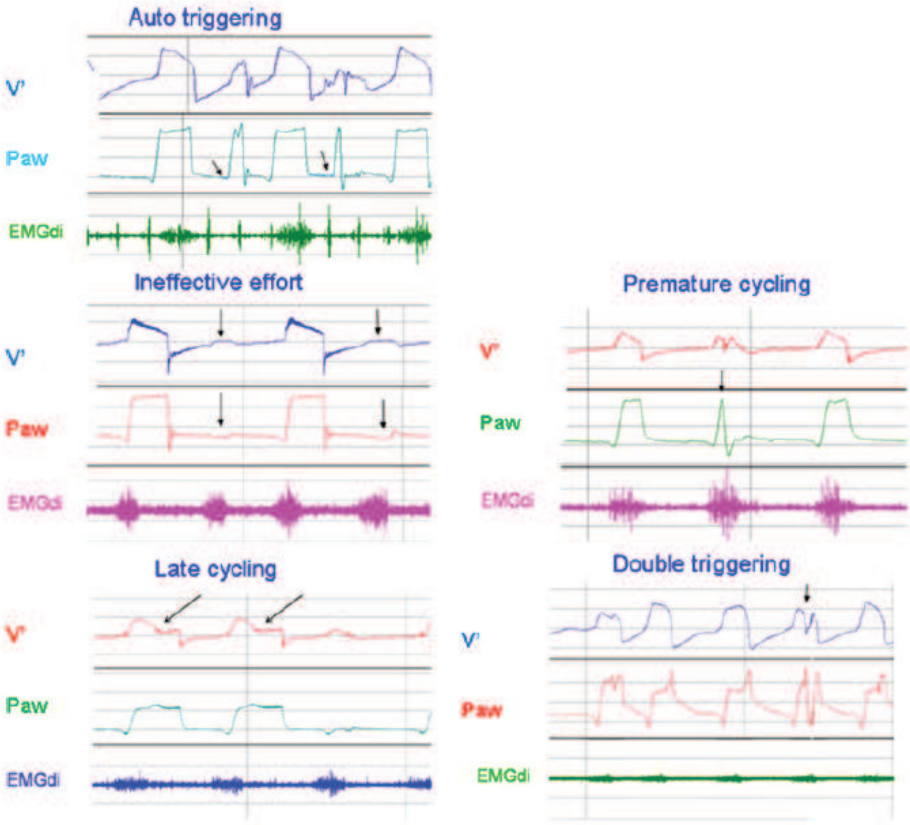

Fig. 2 Representative tracings of the five types of asynchrony. *EMGdi* diaphragmatic electromyography tracing; *Paw* airway pressure; *V'* instantaneous flow. *Downward pointing arrows* indicate relevant events

included. Five were excluded after recording because their electromyography curves were not analyzable. The final study population was therefore 65 patients, whose main clinical characteristics are outlined in Tables 1 and 2. All received NIV via a classical face mask (i.e., oro-nasal, Vygon, Ecouen, France). Inclusion was made 1 ± 0.3 days after initiation of NIV. Thirty-three patients (51%) were hypercapnic ($PaCO_2 > 42$ mm Hg or 5.6 kPa). Causes of ARF were consistent with those reported in the literature: 23 patients (35%) had an acute episode of their chronic pulmonary disease, 18 (28%) received NIV after extubation, 17 (26%) had a community acquired pneumonia, 14 (22%) were post-operative, 2 (3%) had an acute pulmonary edema and 1 (2%) a thoracic traumatism.

Ventilators used were 28 Evita 4 (43%), 19 Evita XL (29%), 14 Servoi (22%), 3 Engström Carestation (5%) and 1 G5 (2%). Ventilator settings and main respiratory parameters are presented in Table 3. Among these respiratory parameters, the only significant difference between NIV0 and NIV+ was the ti_{excess}, with a median of 28% (16–37) and 19% (9–27), respectively.

Comparison of different types of events, with and without the NIV algorithm, is illustrated in Table 4.

Table 1 Demographic and clinical characteristics of the patients ($n = 65$)

Demographics and main respiratory parameters	Mean ± standard deviation
Age (years)	69 ± 12
Men:women (*n*)	41:24
BMI (kg/m^2)	25 ± 5
SAPS II	44 ± 14
BR (*n*/min)	28 ± 8
PaO_2/FiO_2	225 ± 72
$PaCO_2$ (mmHg)	47 ± 15

Values are expressed as mean ± standard deviation
Main respiratory parameters were recorded at study inclusion
BMI body mass index; *SAPS II* simplified acute physiology score II [38, 39]; *BR* breath rate; *FiO_2* inspired fraction of oxygen

Table 2 Chronic conditions

Condition	*n* (%)
Chronic obstructive pulmonary disease	25 (38)
Cardiac insufficiency	9 (14)
Obesity (BMI > 30)	7 (10)
Bronchial carcinoma	2 (3)
Mixed obstructive/restrictive disease	1 (2)
Pulmonary hypertension	1 (2)
Neuromuscular disease	1 (2)

Several chronic conditions can co-exist in a given patient
Values are expressed as number (%)
BMI body mass index

Auto triggering

The number of auto triggerings was significantly lower if the NIV algorithm was activated ($p = 0.01$). If patients are separated into two groups, one with "low" assistance (≤14 cm H_2O) and another with "high" assistance (≥15 cm H_2O), one can observe that the NIV algorithm

Table 3 ventilator settings and main respiratory parameters

Ventilator settings	Mean (SD) or median (25th–75th)	
PSL (cmH_2O)	13 (3)	
PEEP (cmH_2O)	5 (5–7)	
Slope (ms)	200 (100–200)	
Inspiratory trigger		
Flow (l/min) ($n = 64$)	1 (0.3–2)	
Pressure (cm H_2O) ($n = 1$)	−1	
ETS (%PIF)	25	
FiO_2	0.37 (0.1)	
Respiratory parameters during NIV	**NIV0**	**NIV+**
Breath rate (patient)	26 (8)	26 (7)
ti_p (ms)	830 (260)	840 (240)
ti_{excess} (%)	28 (16–37)	19 (9–27)*
VTE		
ml	570 (220)	560 (210)
ml/kg	9 (3)	9 (3)
MV (l/min)	13.4 (5)	13.4 (5)
Leaks		
l/min	4 (1–7)	3.5 (1–7)
% MV	28 (10–56)	23 (9–52)

All values are expressed in mean (standard deviation) or median (25th–75th percentile), according to the parametric or non-parametric nature of their distribution
PSL pressure support level, *PEEP* positive end expiratory pressure; *ETS* expiratory trigger setting; expressed in percentage of peak inspiratory flow (*PIF*); *NIV0 and NIV+* without and with NIV mode respectively; *RRp* respiratory rate of the patient; t_{ip} inspiratory time of the patient; ti_{excess} inspiratory time of the ventilator in excess reported to the ti_p; *VTE* expired tidal volume, expressed in absolute value and in ml/kg of ideal body weight (IBW). Leaks are expressed in absolute value and in percentage of minute ventilation (MV)
* $p < 0.05$ vs. NIV0

Table 4 number of asynchronies with and without NIV mode

	NIV0 Mean ± SD	NIV+ Mean ± SD	NIV0 *n* (%)	NIV+ *n* (%)
Auto triggering	1.2 ± 2.8	0.5 ± 0.8*	14 (22)	10 (15)
Ineffective efforts	1.4 ± 3.1	0.5 ± 1.1*	15 (23)	5 (8)*
Late cycling	0.6 ± 1.6	0.2 ± 0.6*	11 (17)	5 (8)*
Premature cycling	2.1 ± 5	3.3 ± 7	22 (34)	21 (32)
Double triggering	0.2 ± 0.5	0.3 ± 0.8	3 (5)	6 (9)
Asynchrony index (AI)	18 ± 20	19 ± 27	30 (46)	25 (38)
Alleaks	9 ± 12	5 ± 7*	18 (28)	8 (12)*

n Number of patients presenting each type of asynchrony (>1/min) or an AI > 10%
* $p < 0.05$ vs. NIV0

efficiency is higher in the "high" assistance group [delta auto triggering = −0.01 (−0.3; 0.1) and −0.2 (−0.5; 0) auto triggering/min for "low" and "high" assistance, respectively $p = 0.05$)] even if the level of leaks and the incidence of auto triggering is comparable at NIV0 in the two groups.

Ineffective efforts

There were fewer ineffective efforts with the NIV algorithm ($p < 0.001$). Improvement was proportional to the magnitude of ineffective efforts with NIV0 ($r = 0.9$; $p < 0.001$). Fifteen patients (23%) had more than one ineffective effort per minute with NIV0, and six (8%) with the NIV algorithm ($p = 0.007$). NIV algorithm efficiency was higher in the "high" assistance group [delta ineffective effort = −0.02 (−0.3; 0.08) and −0.2 (−1.5; −0.03) ineffective efforts/min for "low" and "high" assistance, respectively $p = 0.03$) even though the incidence of ineffective effort was comparable at NIV0 in the two groups, $p = 0.1$)].

Late cycling

When the NIV algorithm was activated, late cycling decreased significantly ($p = 0.003$). This improvement was correlated with the magnitude of late cycling with NIV0 ($r = 0.9$; $p < 0.001$). Without the NIV algorithm, this type of event was considered as present ($n > 1$) for 11 (17%) patients, and for 5 (8%) with the NIV algorithm ($p = 0.05$). Late cycling was more prevalent in the "high" assistance group [0.03 (0; 0.3) and 0.3(0.04; 1.1) late cycling/min for "low" and "high" assistance, respectively, $p = 0.02$]. When the NIV mode was activated, there was no difference between the two groups.

Premature cycling

The NIV algorithm led to a non-significant trend towards an increase in PC. Twenty-two patients (34%) had PC with NIV0, 21 (32%) with NIV+ ($p = 0.8$).

Double triggering

No difference was observed whether the NIV algorithm was activated or not.

Ti_{excess}

It was significantly lowered when the NIV algorithm was used. The delta ti_{excess} was −14.2% (−20; −5) for Servoi, −4.4% (−9; −2) for Evita 4, and −0.5 (−12; 2) for Evita XL ($p = 0.01$). The correction capacity was higher for the Servoi, versus Evita 4 or Evita XL ($p < 0.05$). Conversely, premature cycling was increased by the NIV algorithm of the Servoi [+1.3 (−0.04; 17)] compared to Evita XL and Evita 4 (0, $p = 0.04$).

Asynchrony index (AI)

No difference was noted in the AI whether or not the NIV algorithm was activated ($p = 0.69$). At NIV0, 30 patients (46%) presented with a severe AI and 25 patients (38%) with NIV+, a non-significant difference.

AIleaks

The AIleaks was significantly associated with the NIV algorithm: when the NIV algorithm was activated, AIleaks was lower [regression coefficient = −4.22; confidence interval (−7; −1.5); $p = 0.002$)] independently of the sequence (NIV+ then NIV0 or NIV0 then NIV+), VTE, respiratory rate or level of leaks. Improvement was correlated to the magnitude of AIleaks with NIV0 ($r = 0.9$; $p < 0.001$).

AIleaks was significantly and independently associated with the pressure support level [regression coefficient = +0.76 by cmH2O of pressure support added; confidence interval (0.2; −1.3); $p = 0.009$]. The NIV algorithm had a higher efficiency in the "high" assistance group [Delta AIleaks = −0.6 (−2.5; 1) and −2.2 (−12; −1.3) % for "low" and "high" assistance, respectively, $p = 0.007$].

Covariance analysis performed on patients with and without the NIV algorithm showed that the level of leaks, expressed in percentage of minute ventilation, was positively and significantly associated with AIleaks in patients in NIV0 conditions [regression coefficient = +0.069 by percent of leaks, confidence interval (0.007–0.13); $p = 0.03$].

However, this correlation did not persist for the same level of leaks with the NIV algorithm activated.

AIleaks, with and without the NIV algorithm, and delta AIleaks were not associated with presence of chronic obstructive pulmonary disease, hypercapnia or type of ventilator.

Discussion

This study is the first to evaluate the clinical effects of ICU ventilator NIV algorithms on patient-ventilator interaction. The main results with the NIV algorithm turned on are the following:

1. The number of patients presenting each type of asynchrony decreased by an average of 50%.
2. Although the specific AIleaks was decreased by 45%, on average, the AI, which reflects overall asynchrony, remained unchanged by NIV algorithms.
3. Some NIV algorithms tend to over-correct ti_{excess}, leading to an increase in the incidence of premature cycling.

Before discussing these results, some limitations of this study should be underlined. First, EMG tracings analysis may be prone to observer interpretation variability. To alleviate this problem, two different investigators, blinded to patient characteristics and whether tracings were acquired during NIV0 or NIV+, performed the analysis. Furthermore, a strict methodology, used in a previous trial, was followed [5]. No inter-observer difference was noted. Moreover, sternocleidomastoid electromyography was used besides diaphragmatic electromyography as a backup in cases where the diaphragmatic signal proved difficult to interpret.

Second, the level of leaks found in our study might not reflect that found in other centers, as the three participating ICUs have a great deal of experience with NIV. Of note, the same three centers performed a recent observational study on asynchrony during NIV [5], and the patient populations were comparable, as were the levels of leaks and severity of asynchronies. Third, five different ventilators were used for this study, which could have influenced results because of their different NIV algorithm performances. Bench test results of these machines showed that their NIV algorithms corrected part or all of leak-associated asynchronies, but with variable efficacy [10]. In this study, one of the ventilators' NIV algorithm (Servoi) had a different behavior with inspiratory time in excess and premature cycling. This ventilator was more efficient to correct ti_{excess}, but induced more premature cycling. Finally, only 65 patients were included, which does not allow a precise sub-group analysis by respiratory mechanics category. As each patient is his own control, this could have influenced results.

Studies have shown that during NIV, auto-triggering, ineffective efforts and late cycling were associated with leaks [6, 7]. The same observation was made in the present study, confirming the findings of our previous observational study [5].

Because only these asynchronies are associated with leaks, and partially corrected by NIV algorithms, the specific AIleaks could be used when one is interested in asynchronies favored by leaks. Assessment of global asynchrony still requires the use of the AI.

The main finding of this study was that activating the NIV algorithm has a clear and significant effect on the number and severity of asynchrony events resulting from leaks. These results are consistent with the findings of a recent bench model study in which NIV algorithms were shown to correct such events, albeit with large variation between machines [10]. Moreover, the number of AIleaks was higher and the NIV algorithm more efficient in the group with "high" assistance. In the studies by Thille et al. [14, 15], the level of pressure support was correlated with the asynchrony index, but was independent of the level of leaks. Patient-ventilator asynchrony was found to be correctible by reducing the level of pressure support and shortening ventilator insufflation time [15]. This approach is also valid during NIV. However, the additional problem of leaks needs to be addressed. Therefore, NIV algorithms could provide an added benefit for optimizing patient-ventilator interaction, and this study suggests their efficacy in pursuing that goal. However, the approach is different from one ventilator to another. Some ventilators (the Servoi in this study) tend to over-correct ti_{excess}, leading to an increase in the incidence of premature cycling. This may explain why the NIV algorithm can partially correct the AIleaks while the global AI remains unchanged. This difference between ventilators was not apparent in our previous bench testing [10], suggesting that even if the trend is the same, a ventilator can have a different behavior in bench testing and in the clinical setting.

In invasive ventilation, asynchronies are a risk factor for an increase in the duration of mechanical ventilation [14]. An adverse impact of asynchronies on patient outcome has not been demonstrated with NIV [5]. Nonetheless, since patient intolerance to the technique has been shown to be a risk factor for NIV failure [11, 16], one can at least hypothesize that decreasing asynchronies during NIV could be a part of a strategy to maximize the chances of its success. While clearly representing a step in the right direction, NIV algorithms probably need some more fine-tuning so that all machines can provide optimal patient–ventilator synchrony in such leak-prone conditions. Technologies derived from those of home ventilators might be part of the solution, as these machines have a long history of dealing with major leaks [10].

Conclusion

Activating the NIV algorithm on ICU ventilators during the application of NIV for ARF decreases the incidence of those asynchronies typically associated with leaks, while not necessarily changing the overall asynchrony situation. Part of this mixed message comes from the varying technological solutions in different machines, the correction of one asynchrony leading to the increase of another. Therefore, future studies should explore whether

a more homogenous approach among manufacturers or resorting to solutions used in home ventilators could help make further progress in harmonizing patient-ventilator synchrony during NIV.

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ELECTRONIC SUPPLEMENTAL MATERIAL

Performance of noninvasive ventilation algorithms on ICU ventilators during pressure support: a clinical study

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Material and methods

Criteria for initiating NIV: they followed the usual practice guidelines of each center, requiring at least two of the following:

- worsening dyspnea over the last ten days in patients with chronic respiratory failure;
- respiratory rate > 25 /min;
- arterial pH < 7.35;
- $PaCO_2$ > 50 mm Hg (6.6 KPa)
- PaO_2 < 50 mmHg (6.6 KPa)

Measured parameters: The following parameters were measured: respiratory rate, expired tidal volume (VTE), minute volume, leaks at the mask (using the equation Leaks (L/min) = [VTinspired-VTexpired] x Respiratory rate), inspiratory times of the patient (ti_p) and of the ventilator (ti_v), and asynchrony events (auto-triggering, ineffective triggering, late cycling, premature cycling and double triggering). Measurements were averaged over 50 cycles 10 consecutive and analyzable cycles at 5, 10, 15 and 20 minutes. All asynchrony events were recorded and averaged by minute.

The respiratory parameters and asynchrony events were measured by analysis of tracings from airway pressure (Paw), flow, and surface electromyographic activity of the diaphragm as described in a previous study [1] to which we added surface electromyographic activity of the sternocleidomastoid. Briefly, Paw and flow were

recorded over the two NIV periods between the y piece and the mask, using a differential pressure transducer (Validyne MP45, ± 100cm H2O, Northridge, CA, USA) and a Fleisch No 2 pneumotachograph (Fleisch, Lausanne, Switzerland), respectively. Simultaneously, diaphragmatic electromyography was recorded with surface electrodes placed bilaterally over the costal margin, one reference electrode being placed over the sternum [2]. Sternocleidomastoid electromyography was recorded using two surface electrodes on the muscle body, on the neck side of the patient, one reference electrode being placed over the sternum. Their analog signals were first filtered and digitized at a sampling rate of 200 Hz for pressure and flow, and 500 Hz for the EMGdi by means of the Biopac EMG module (Biopac Systems Inc., Goleta, CA, USA). The signals were rectified, then integrated. Volumes were determined by integration of the flow signal. The neural inspiratory time ti_p (figure 1) was defined as the time interval between the beginning and the end of the diaphragmatic activity (start of the ascent and start of the rapid decrease of the signal respectively). The diaphragmatic electromyographic signal was used preferentially for this determination, the sternocleidomastoid signal being used as a backup in cases where the diaphragmatic signal proved difficult to interpret (e.g. presence of abdominal muscle activity, where we used sternocleidomastoid EMG to determine the end of the inspiration). Inspiratory time of the ventilator (Ti_v) was defined as the time interval between the beginning of patient inspiration and the return to zero of the flow signal. The inspiratory time in excess (ti_{excess}) was defined as following (Main document, figure 1):

$$ti_{excess}\ (\%) = [(ti_v - ti_p) / ti_p] \times 100$$

Asynchrony events were defined according to our previous study [1] (Main document, figure 2): ***auto-triggering (AT)*****:** a cycle delivered by the ventilator in the absence of

inspiratory electromyographic signal; ***ineffective effort (IE)***: an inspiratory electromyographic signal not followed by an assisted cycle; ***late cycling (LC)****:* a cycle with a ventilator inspiratory time greater than twice neural inspiratory time; ***premature cycling (PC):*** a cycle with a ventilator inspiratory time less than neural inspiratory time; ***double triggering (DT)****:* two cycles separated by a very short inspiratory time, during the same inspiratory electromyographic signal. Each type of event was considered present if it occurred an average of > 1/min. over the 30 min. recording period. For each type of event and for inspiratory time in excess (ti_{excess}), the difference between NIV+ and NIV0 was evaluated. A global asynchrony index (AI), computed as previously published [1, 3], defined as the total number of the various events described above divided by the total number of non-triggered and triggered ventilatory cycles. Therefore AI (%) = number of events / (ineffective effort + ventilator cycles) x 100 = [(auto triggering + ineffective effort + late cycling + premature cycling + double triggering) / (ineffective effort + Respiratory rate vent)] x 100. An AI > 10 % was considered as severe. This index was originally designed for intubated patients. In the present study on NIV, the determinants of asynchrony influenced with leaks (ineffective efforts, auto triggering and late cycling) [1, 4, 5] were explored, by defining an AI specific to leaks (AI*leaks*). Auto triggering is more often directly caused by leaks, whereas late cycling and ineffective efforts can also be favored by respiratory mechanics and or inappropriate settings. Ineffective efforts are not a direct consequence of leaks, but more of late cycling, itself caused by leakage. This specific index was computed as follows: AI*leaks* = number of events linked with leaks / (ineffective breaths + ventilator cycles) x 100 = [(auto triggering + ineffective effort + late cycling) / (ineffective effort + Respiratory rate ventilator)] x 100.

All tracings were analyzed by two investigators (L.V. and L.P.).

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Article 4 :

Evaluation sur banc d'essai et clinique de la synchronisation patient-ventilateur en VNI avec l'utilisation de ventilateurs de réanimation, de transport et dédiés à la VNI.

CHEST Original Research
CRITICAL CARE

Patient-Ventilator Asynchrony During Noninvasive Ventilation

A Bench and Clinical Study

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Background: **Different kinds of ventilators are available to perform noninvasive ventilation (NIV) in ICUs. Which type allows the best patient-ventilator synchrony is unknown. The objective was to compare patient-ventilator synchrony during NIV between ICU, transport—both with and without the NIV algorithm engaged—and dedicated NIV ventilators.**
Methods: **First, a bench model simulating spontaneous breathing efforts was used to assess the respective impact of inspiratory and expiratory leaks on cycling and triggering functions in 19 ventilators. Second, a clinical study evaluated the incidence of patient-ventilator asynchronies in 15 patients during three randomized, consecutive, 20-min periods of NIV using an ICU ventilator with and without its NIV algorithm engaged and a dedicated NIV ventilator. Patient-ventilator asynchrony was assessed using flow, airway pressure, and respiratory muscles surface electromyogram recordings.**
Results: **On the bench, frequent auto-triggering and delayed cycling occurred in the presence of leaks using ICU and transport ventilators. NIV algorithms unevenly minimized these asynchronies, whereas no asynchrony was observed with the dedicated NIV ventilators in all except one. These results were reproduced during the clinical study: The asynchrony index was significantly lower with a dedicated NIV ventilator than with ICU ventilators without or with their NIV algorithm engaged (0.5% [0.4%-1.2%] vs 3.7% [1.4%-10.3%] and 2.0% [1.5%-6.6%], $P < .01$), especially because of less auto-triggering.**
Conclusions: **Dedicated NIV ventilators allow better patient-ventilator synchrony than ICU and transport ventilators, even with their NIV algorithm. However, the NIV algorithm improves, at least slightly and with a wide variation among ventilators, triggering and/or cycling off synchronization.**
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Abbreviations: AI = asynchrony index; ICUniv− = ICU ventilator with the noninvasive ventilation algorithm turned off; ICUniv+ = ICU ventilator with the noninvasive ventilation algorithm turned on; NIV = noninvasive ventilation; NIVv = dedicated noninvasive ventilation ventilator; PEEP = positive end-expiratory pressure; TD = triggering delay; TIexcess = insufflation time in excess; TIsim = simulated active inspiration time; TIvent = time between the beginning of a simulated inspiratory effort and the end of the ventilator's insufflation

Noninvasive ventilation (NIV) has become a standard of care for the management of many causes of acute respiratory failure.[1-3] During NIV, the unavoidable presence of leaks around the mask[4] can interfere with the ventilator performance. Expiratory leaks can mimic an inspiratory effort for the ventilator, leading to auto-triggering[5]; and inspiratory leaks can mimic a sustained inspiration, leading to delayed cycling.[6] Not surprisingly, patient-ventilator asynchronies have, therefore, been reported to occur with a high incidence during NIV in critically ill patients.[7]

Different ventilators are now used to conduct NIV in ICU: ICU ventilators,[2] dedicated NIV ventilators,[8]

For editorial comment see page 274

and also transport ventilators when needed.[9-11] Most ICU ventilators were initially built to work without any leak, at least in adults, and are prone to be disrupted

by the presence of leaks during NIV.[12] To address this issue, manufacturers have implemented NIV algorithms (so called "NIV modes") on the latest generation of ICU ventilators to compensate and better manage the leaks. Both bench[12,13] and clinical[14] studies assessing the performance of NIV algorithms on ICU ventilators have shown mixed results, partly due to large variations among the ventilators, making it difficult to draw an overall conclusion. Dedicated NIV ventilators stem from bilevel home ventilator technology, which has been particularly oriented toward leakage management and comfort. Some bench studies suggested that a dedicated NIV ventilator could produce better performance and synchronization than ICU ventilators in the presence of leaks.[13,15] However, no bench model concerning ventilator synchronization during NIV has been clinically validated, raising the question of their clinical relevance in critically ill patients. Consequently, the kind of ventilator that allows the best synchronization during NIV in the ICU is still unknown. In some areas, NIV is mainly delivered with dedicated NIV ventilators,[8] whereas in other countries ICU ventilators are almost exclusively preferred,[2] and this distribution reflects local habits rather than an evidence-based approach.

The purpose of this study was to compare patient-ventilator synchronization during NIV using ICU and transport ventilators with or without their NIV algorithm, and finally dedicated NIV ventilators. We designed a bench model to assess ventilator synchronization with a simulated inspiratory effort in different leak conditions, simulating the different challenges to be faced by the ventilator. Furthermore, we conducted a clinical study in critically ill patients to compare the incidence of patient-ventilator asynchrony between ICU ventilators with and without their NIV algorithm engaged, and a dedicated NIV ventilator.

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Materials and Methods

This study involved a bench part and a clinical part. An extensive description of both the bench and clinical protocols is provided in e-Appendix 1.

Bench Study

All 19 ventilators tested are reported in Table 1 and included eight ICU ventilators, five transport ventilators, and six dedicated NIV ventilators. The test lung, an Active Servo Lung 5000 (ASL 5000; IngMar Medical, Ltd), was used to simulate a moderate inspiratory effort in the presence of an 80 mL/cm H_2O respiratory system compliance and 10 cm H_2O/L/s resistance to mimic a mild obstructive condition. The simulated respiratory rate was 15 breaths/min and the inspiratory time 0.8 s. Three leak conditions were generated (Fig 1A): absence of leak, continuous leak (to reveal triggering asynchronies during expiratory leak), and inspiratory leak (to reveal cycling-off asynchronies). For this last experiment, the leak started at a pressure corresponding to a water column of 7 cm H_2O, as detailed in e-Appendix 1. The inspiratory leak was characterized by a nonlinear pressure-flow relationship with a flow varying from 0 to 22 L/min for a pressure from 7 to 15 cm H_2O. The continuous (expiratory) leak was characterized by a flow of 16 L/min at 5 cm H_2O pressure.

Ventilators were set in pressure support ventilation, with a pressure support level at 15 cm H_2O and a positive end-expiratory pressure (PEEP) at 5 cm H_2O. ICU and transport ventilators were tested with and without their NIV algorithm engaged, except the Elisee 250, whose NIV algorithm cannot be turned off. Data were acquired at 512 Hz from ASL 5000 and stored in a laptop computer for subsequent analysis (Acqknowledge 3.7.3; BIOPAC Systems, Inc). Inspiratory triggering synchronization was assessed using the triggering delay, the triggering pressure-time product, and the incidence of auto-triggering, expressed as a percentage and calculated as follows: auto-triggering incidence (%) = (auto-triggered cycles/total ventilator cycles) × 100. The pressurization was assessed using the pressure-time product at 300 milliseconds. Cycling synchronization was assessed by determining ventilator insufflation time in excess (TIexcess), expressed as a percentage and calculated as follows: $TIexcess = [(TIvent - TIsim)/TIsim] \times 100$, where TIvent is the time between the beginning of the simulated inspiratory effort and the end of the ventilator's insufflation, and TIsim the simulated active inspiration time. Delayed cycling was defined by a $TIvent \geq 2\ TIsim$ and premature cycling by a $TIvent \leq 2/3\ TIsim$.

Clinical Study

A prospective, randomized, crossover study was conducted in two university hospital ICUs. The protocol was approved by the ethics committee CPP-Ile-de-France IX (number: 08-021), and informed consent was obtained from all patients. We included 15 patients in the ICU receiving NIV in pressure support ventilation mode with PEEP via a standard oronasal mask. The ventilator settings chosen by the clinician in charge of the patient were kept identical for the study. Three consecutive NIV sessions were applied in a random order, using the same oronasal mask: (1) use of an ICU ventilator whose NIV algorithm has been turned off

Table 1—*Bench Study: Characteristics of the ICU, Transport, and NIV Ventilators Tested in the Bench Study*

Ventilator	Supplier	Use	Gas Source	Circuit	NIV Mode	ET Range	IT Range
Avea	CareFusion	ICU	Pressurized	Double	Manual	5%-45%	0.1-20 L/min
Engstrom	GE Healthcare	ICU	Pressurized	Double	Manual	5%-50%	1-9 L/min; −1 to −10 cm H_2O
Evita XL	Dräger	ICU	Pressurized	Double	Automatic	Automatic	0.3-15 L/min
G5	Hamilton Co	ICU	Pressurized	Double	Manual	5%-70%	0.5-15 L/min
PB840[a]	Covidien	ICU	Pressurized	Double	Manual	1%-80%	0.2-20 L/min
Servo-i	MAQUET GmbH & Co KG	ICU	Pressurized	Double	Manual	1%-40%	0%-100%; −20 to 0 cm H_2O
V500	Dräger	ICU	Pressurized	Double	Automatic/manual	Automatic; 5%-70%	Automatic; 0.2-15 L/min
Vela	CareFusion	ICU	Turbine	Double	Manual	5%-40%	1-8 L/min
Elisee 250	ResMed	Transport	Turbine	Double	Automatic/manual	Automatic; 1%-6%	Automatic
Medumat	Weinmann Medical Technology	Transport	Pneumatic	Single	Automatic	5%-50%	1-15 L/min
Oxylog 3000	Dräger	Transport	Pneumatic	Single	Automatic	Automatic	Automatic
Supportair	Covidien	Transport	Turbine	Single	Manual	5%-95%	01-05
T1	Hamilton Co	Transport	Turbine	Double	Manual	5%-80%	1-20 L/min
BiPAP Vision	Philips Respironics	NIV	Turbine	Single	Automatic	Automatic	Automatic
Carina	Dräger	NIV	Turbine	Single	Automatic	Automatic	Analogical (sensible/normal)
Trilogy 100	Philips Respironics	NIV	Turbine	Single	Automatic	Automatic	Automatic
V60	Philips Respironics	NIV	Turbine	Single	Automatic	Automatic	Automatic
Vivo 40	Breas	NIV	Turbine	Single	Automatic	Automatic	Automatic
VPAP 4	ResMed	NIV	Turbine	Single	Automatic	Automatic	Automatic

ET = expiratory trigger, expressed as a percentage of peak inspiratory flow; IT = inspiratory trigger; NIV = noninvasive ventilation.
[a]Version comprising both an NIV mode and leak compensation.

(ICUniv−), (2) use of an ICU ventilator whose NIV algorithm has been turned on (ICUniv+), and (3) use of a dedicated NIV ventilator (NIVv). Each session was 20 min long. ICU ventilators used in the clinical study were: Evita XL or EVITA 4 (Dräger) (n = 12) and Engstrom Carestation (GE Healthcare) (n = 3). The dedicated NIVv was the BiPAP Vision (Philips Respironics). We selected this ventilator because it is widely used in ICUs using NIV ventilators and also because it has been used in many clinical and physiologic studies concerning NIV. Flow, airway pressure, and diaphragmatic and inspiratory neck muscles surface electromyograms were continuously recorded throughout the three NIV sessions and stored in a laptop for subsequent analysis, as described in e-Appendix 1. All tracings were analyzed by one investigator (G. C.). The methodology used was previously described without noticing any interobserver difference,[7,14] and allowed the quantification of major asynchrony events (ineffective triggering, double-triggering, auto-triggering, premature cycling, and delayed cycling) (Fig 1B). A global asynchrony index (AI), expressed as a percentage, was computed as follows[16]: AI (%) = (number of asynchronies/[ineffective breaths + ventilator cycles]) × 100.

Statistics

Statistical analyses were performed with Statistical Package for the Social Sciences (version 16.0, SPSS). Continuous data are expressed as the median (25th-75th percentile). In both the bench and clinical study, the variables did not display a normal distribution, so only nonparametric tests, detailed in e-Appendix 1, were used. A P value of < 0.05 was considered statistically significant.

Results

Bench Study

Triggering Delay: The ICU and transport ventilators with their NIV algorithm turned off in the absence of leaks exhibited a total triggering delay (TD) of 117 milliseconds (99-131 milliseconds) and 143 milliseconds (114-174 milliseconds), respectively ($P = .37$) (Fig 2).The addition of inspiratory leaks did not significantly modify these values except for the Engstrom, G5, and T1, which had an increased TD, and the Medumat, which showed a reduced TD. Turning on the NIV algorithm while maintaining inspiratory leaks led to different behaviors among ICU and transport ventilators: TD significantly increased for five ventilators (Medumat, Evita XL, Servo-i, V500, Supportair), decreased for three (Engstrom, PB840, T1), and was not modified for the others. In this last condition, the TD of ICU, transport, and dedicated NIV ventilators were 107 (83-120), 126 (112-190), and 125 (102-145) milliseconds, respectively ($P > .05$ for every intergroup comparison). When NIV algorithms were used in the presence of inspiratory leaks, six ICU ventilators (Avea, Engstrom, PB840, Servo-i, V500, Vela), two transport ventilators (Elisee 250, Supportair), and two NIV ventilators (BiPAP Vision, V60) exhibited a TD < 117 milliseconds (ie, the median TD of ICU ventilators with the NIV algorithm turned off in absence of leaks). The additional assessment of the triggering pressure-time product is reported in e-Appendix 1 and e-Figure 1.

Auto-Triggering: Occurrence of auto-triggering was assessed during the presence of continuous leaks (Fig 3). Expiratory leaks induced an incidence of auto-triggering between 0% and 100% among ICU and transport ventilators when their NIV algorithm was

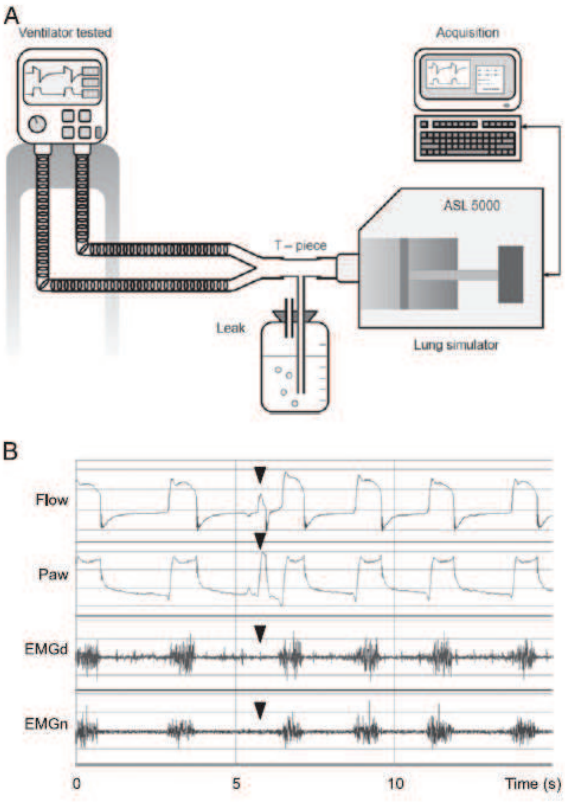

FIGURE 1. Experimental protocols. A, Bench study experimental design. To experimentally reproduce noninvasive ventilation (NIV) conditions with calibrated leaks, we placed a T-piece between the ASL5000 (lung simulator) and the ventilator circuit. Three situations were generated: no leak, in which the free extremity of the T-piece was closed; inspiratory leak, in which the free extremity of the T-piece was connected to a tube immersed in a 7 cm H_2O column, allowing leaks to occur during insufflation only when the pressure in the circuit was higher than the height of the water column; and continuous leak using the same experimental assembly without water in the receptacle, allowing leaks to occur during the whole respiratory cycle. B, Clinical study representative record of an auto-triggered cycle. EMGd = diaphragmatic electromyogram; EMGn = neck muscles electromyogram; Paw = airway pressure.

turned off. The activation of the NIV algorithm led to a heterogeneous response among these ventilators: the incidence of auto-triggering fell to or remained at 0% for three ICU ventilators (PB840, Servo-i, V500) and three transport ventilators (Elisee 250, Supportair, T1), was not modified for one ICU ventilator (Avea), and decreased slightly for the other ICU and transport ventilators. By contrast, no auto-triggering occurred with any NIV ventilator.

Cycling and Insufflation Time: ICU and transport ventilators without their NIV algorithm in the absence of leaks exhibited a Tiexcess of 32% (30%-34%) and 49% (24%-75%), respectively ($P = .93$) (Fig 4). Inspiratory leaks led to a significant increase in insufflation time for six ICU ventilators (Avea, Engstrom, G5, PB840, Servo-i, Vela) and all four transport ventilators whose NIV algorithm can be turned off. The NIV algorithms generally minimized the insufflation time, which remained significantly higher than without leaks for only two ICU ventilators (Avea, G5) and three transport ventilators (Oxylog 3000, Supportair, T1). With NIV algorithm and inspiratory leaks, ICU, transport, and dedicated NIV ventilators exhibited a Tiexcess of 34% (29%-43%), 37% (25%-43%), and 37% (18%-49%), respectively. In this condition, the Tiexcess was < 32% for four ICU ventilators (Engstrom, Evita XL, Servo-i, V500), two transport ventilators (Medumat, Supportair), and three dedicated NIV ventilators (BiPAP Vision, Trilogy 100, V60).

During inspiratory leaks when NIV algorithms were turned off, delayed cycling occurred with four ICU ventilators (Avea, G5, PB840, Vela) and three transport ventilators (Medumat, Oxylog 3000, T1). The activation of the NIV algorithm eliminated delayed cycling for all of these ventilators but one (G5). However, the NIV algorithm of the Servo-i overcorrected the Tiexcess (−4%). Concerning dedicated NIV ventilators subjected to inspiratory leaks, one of them (VIVO 40) exhibited delayed cycling.

We also assessed the ability of the ventilators to pressurize the airway in the first 300 milliseconds with or without leaks. For the sake of simplicity, these data are only shown in e-Appendix 1 and e-Figure 2.

Clinical Study

Fifteen patients of median age 68 years old (61-76 years) were included, 13 men and two women, with a median BMI of 24 kg/m² (20-27 kg/m²). At inclusion, Simplified Acute Physiology Score II was 47 (32-62) and arterial blood gas levels were as follows: pH = 7.36 (7.29-7.42), $Paco_2$ = 48 mm Hg

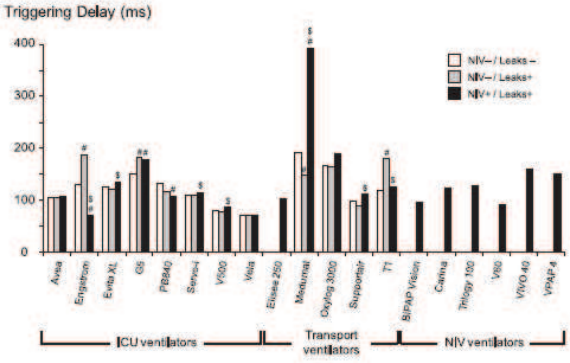

FIGURE 2. Bench study triggering delay. Representation of the triggering delay for ICU and transport ventilators with their NIV algorithm turned off in the absence of any leak (NIV−/Leaks−, white bars), then in the presence of inspiratory leaks (NIV−/Leaks+, gray bars); and for ICU and transport ventilators with their NIV algorithm turned on as well as for NIV ventilators in the presence of inspiratory leaks (NIV+/Leaks+, black bars). # $P < .05$ vs NIV−/Leaks−. \$ $P < .05$ vs NIV−/Leaks+. See Figure 1 legend for expansion of abbreviation.

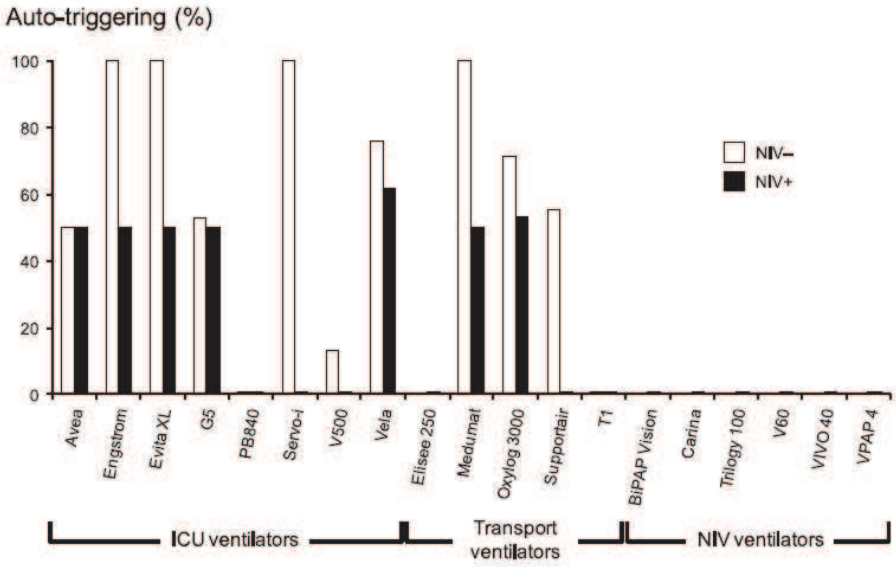

FIGURE 3. Bench study incidence of auto-triggering during continuous leaks. Incidence of auto-triggering is represented as a percentage of the total ventilator cycles ([Auto-triggered cycles]/[total ventilator cycles] × 100) during continuous leaks with ICU and transport ventilators without NIV algorithm (NIV−, white bar) and with the same ventilators with the NIV algorithm turned on, and with NIV ventilators (NIV+, black bar). The activation of the NIV algorithm on ICU and transport ventilators unequally led to an improvement in inspiratory triggering synchronization, whereas no auto-triggering occurred with any NIV ventilator. See Figure 1 legend for expansion of abbreviation.

(41-63 mm Hg), Pao_2/Fio_2 = 206 mm Hg (183-252 mm Hg). Patients had spent one median day (0.3-1.0 days) under NIV before inclusion. Indications for NIV were the following: to avert respiratory failure after extubation (n = 5), exacerbation of COPD (n = 4), cardiogenic pulmonary edema (n = 3), community-acquired pneumonia (n = 2), and post thoracic surgery (n = 1). Eight patients (53%) had COPD. Ventilator settings were pressure support level = 10 cm H_2O (8-11 cm H_2O), PEEP = 4 cm H_2O (4-5 cm H_2O), inspiratory trigger = 1 L/min (1-2 L/min), pressurization slope = 100 milliseconds (100-100 milliseconds), and Fio_2 = 40% (30%-50%). There was no significant difference between the three NIV sessions regarding ventilator settings, respiratory parameters, and the measured level of leaks (Table 2). ICU ventilators used in the clinical study had a similar response to leaks as during the bench study in terms of asynchrony: a propensity to auto-triggering with expiratory leaks, partially corrected by the NIV algorithm, but no delayed cycling with the NIV algorithm and inspiratory leaks (Figs 3, 4).

Patient-Ventilator Synchrony: The asynchrony index (AI) did not significantly differ when using ICU ventilators without (ICUniv−) or with (ICUniv+) their NIV algorithm engaged, 3.7% (1.4%-10.3%) vs 2.0% (1.5%-6.6%), respectively, P = .118. By contrast, AI was significantly lower with NIVv (0.5% [0.4%-1.2%]) than with both ICUniv− and ICUniv+ (P = .001 for both comparisons) (Fig 5). The incidence of each asynchrony during the three NIV sessions is represented in Figure 6. Auto-triggering had the highest incidence. The incidence of auto-triggering, however, was significantly lower with NIVv than with ICUniv− and ICUniv+, 0.1/min (0.1-0.1/min) vs 0.5/min (0.1-1.1/min) and 0.3/min (0.1-1.2/min), $P < .001$, and the proportion of patients who exhibited a high incidence of auto-triggering (> 1/min) was significantly lower with NIVv than with ICUniv− and ICUniv+ (Table 3). Four patients (27%) had an AI > 10% with ICUniv−, two (13%) with ICUniv+, and none with NIVv (P = .091). The level of leaks throughout the clinical study was noticeably high in these two last patients (14 and 16 L/min, respectively). The proportion of patients who exhibited at least one asynchrony with a high incidence (> 1/min) was significantly higher with ICUniv− and ICUniv+ than with NIVv (Table 3).

DISCUSSION

To our knowledge, this study is the first to compare patient-ventilator synchronization during NIV between ICU, transport, and dedicated NIV ventilators, with both a bench and a clinical evaluation. The observations made with these two approaches were consistent, offering a strong validation of the bench model, a logical explanation for the clinical data, and

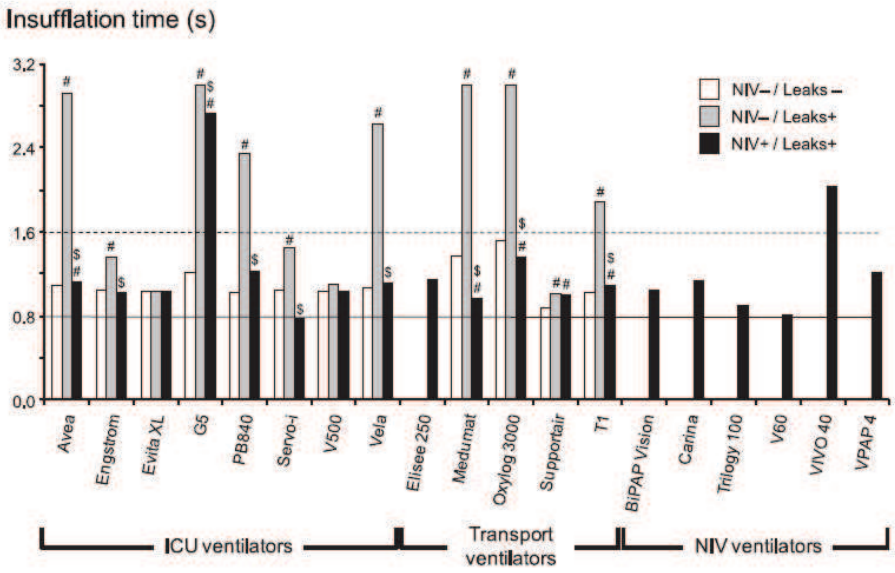

FIGURE 4. Bench study on the effect of inspiratory leaks on insufflation time. Representation of the insufflation time for ICU and transport ventilators without their NIV algorithm in the absence of leak (NIV−/Leaks−, white bars), then in the presence of inspiratory leaks (NIV−/Leaks+, gray bars); and for ICU and transport ventilators with their NIV algorithm turned on as well as for dedicated NIV ventilators in the presence of inspiratory leaks (NIV+/Leaks+, black bars). The simulated inspiratory time was 0.8 s (solid line). When insufflation time reached 1.6 s (dotted line) it corresponded to delayed cycling. For ICU and transport ventilators, the introduction of inspiratory leaks led to an increase in insufflation time when the NIV algorithm was turned off. This prolongation of insufflation due to leaks was partly and unequally minimized by the NIV algorithm. #$P < .05$ vs NIV−/Leaks−, $$P < .05$ vs NIV−/Leaks+. See Figure 1 legend for expansion of abbreviation.

lending strength to the main results of this study, which are:

- In NIV conditions, most dedicated NIV ventilators allowed better patient-ventilator synchronization than ICU and transport ventilators, even when the NIV algorithm was engaged, especially regarding the risk of auto-triggering.
- Most of the dedicated NIV ventilators exhibited a synchronization performance in the presence of leaks equivalent to that of the ICU ventilators in absence of leaks.
- Synchronization performance in the presence of leaks remains heterogeneous among ICU as well as transport ventilators, and each machine should be considered individually.
- The NIV algorithm usually improved, at least slightly, the triggering and/or cycling synchronization of ICU and transport ventilators in the presence of leaks.

Table 2—*Clinical Study: Main Respiratory Parameters*

Respiratory Parameters	ICUniv−	ICUniv+	NIVv	*P* Value
RRp, per min	29 (22-31)	27 (22-31)	26 (24-30)	.982
Tip, ms	780 (599-914)	674 (558-957)	749 (629-923)	.057
Tiexcess, %	14 (4-24)	12 (6-23)	13 (11-21)	.344
V_{TE}, mL	467 (269-633)	465 (322-548)	487 (278-539)	.931
V_{TE}, mL/kg	6.5 (4.3-9.4)	6.9 (4.6-8.3)	7.0 (4.6-9.0)	.797
$\dot{V}_E$, L/min	11.5 (8.7-15.5)	10.3 (9.2-16.7)	10.6 (8.6-14.0)	.683
Leaks, L/min	6.3 (4.3-10.8)	6.2 (2.6-12.1)	7.3 (3.0-11.7)	.947
Leaks, % $\dot{V}_E$	55 (39-101)	47 (26-113)	81 (16-121)	.612

Main respiratory parameters recorded throughout the three NIV sessions during the clinical study. ICUniv− = NIV session using an ICU ventilator whose NIV algorithm has been turned off; ICUniv+ = NIV session using an ICU ventilator whose NIV algorithm has been turned on; NIVv = NIV session using a dedicated NIV ventilator; RRp = patient's respiratory rate measured with the use of the electromyogram signal; Tiexcess = percentage of insufflation time that exceeds the neural inspiratory time; Tip = patient's neural inspiratory time; $\dot{V}_E$ = minute ventilation; V_{TE} = expired tidal volume. See Table 1 legend for expansion of other abbreviation.

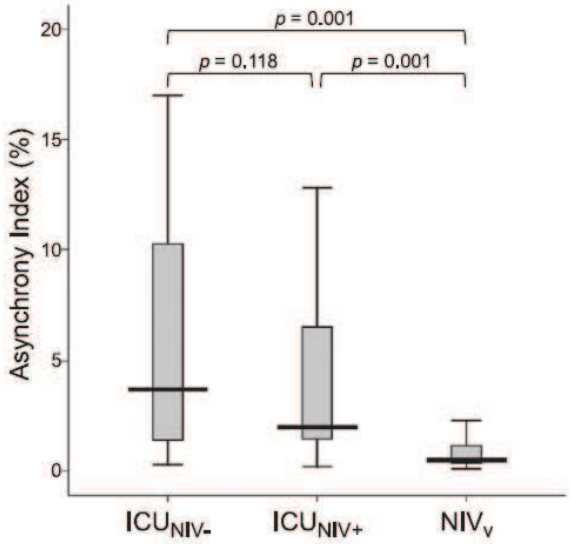

FIGURE 5. Clinical study asynchrony index during the three NIV sessions. The box plots represent the asynchrony index (thick horizontal bar: median; extremities of the boxes: 25th and 75th percentiles; thin horizontal bars: fifth and 95th percentiles) during each 20-min NIV session: ICU_{NIV-}, ICU_{NIV+}, and NIV_V. The asynchrony index was significantly lower with NIV_V than with ICU_{NIV-} and ICU_{NIV+}. ICU_{NIV-} = ICU ventilator with NIV algorithm turned off; ICU_{NIV+} = ICU ventilator with NIV algorithm turned on; NIV_V = dedicated NIV ventilator. See Figure 1 legend for expansion of abbreviation.

Patient-Ventilator Interactions During NIV

Patient-ventilator asynchrony is frequent during both invasive[16,17] and noninvasive[7,14] mechanical ventilation. However, the respective proportion of each type of major asynchrony markedly differs between these two techniques. During invasive mechanical ventilation, ineffective effort represents the most prevalent asynchrony.[16,18] Its occurrence is largely favored by overassistance and can frequently be avoided by reducing the amount of support both in terms of tidal volume and inspiratory time.[19,20] By contrast, during NIV, additional asynchronies, especially auto-triggering and delayed cycling, are induced by the presence of leaks around the mask[4,7] and reflect more the ventilator's ability to manage leaks than the settings chosen by the clinician. Our bench study showed a wide variation in this ability among ICU ventilators and their NIV algorithms, which is consistent with previous bench studies.[12,13] More interestingly, our bench results were also well reproduced during our clinical study. In fact, auto-triggering represented the most frequent asynchrony with ICU ventilators used in the clinical study, as predicted during their bench evaluation. Furthermore, there was a trend toward less asynchrony with the NIV algorithm, which usually minimized asynchronies during the bench study. Vignaux et al[14] assessed the impact of the NIV algorithm on the incidence of patient-ventilator asynchronies during NIV in a clinical study involving 65 patients and five ICU ventilators. Without the NIV algorithm engaged, 46% of the patients had an AI > 10%. The NIV algorithm permitted a decrease in the incidence of asynchronies due to leaks but without a decrease in the overall incidence of patient-ventilator asynchronies (38% vs 46%, $P = .69$), due to a high incidence of asynchronies not directly related to leaks. We report a lower proportion of patients exhibiting an AI > 10% due to a lower incidence of some major asynchronies. Several reasons explain this discrepancy. First, the level of assistance in our study was lower than the one observed in the study by Vignaux et al,[14] leading to a lower tidal volume, which might explain our low incidence of ineffective efforts.[20] Second, we have modified the definition of premature cycling, considering that the previous one was too sensitive in terms of clinical relevance and what can be considered as a "major" patient-ventilator asynchrony. This definition modification has automatically led to less recorded premature cycling, so to a lower AI. Third, the ICU ventilators used in our clinical assessment had the same behavior during our bench evaluation: a propensity to auto-triggering with expiratory leaks, but no delayed cycling in the presence of inspiratory leaks. Although the strength of our bench model was to assess separately the impact of expiratory and inspiratory leaks on triggering and cycling synchronizations, respectively, the originality of our clinical study was to use ICU ventilators that had the same behavior during their bench evaluation. This led to intelligible results and gave a mutual validation to the two assessments. In the meantime, as a part of this behavior was to avoid delayed cycling, this logically led to a decrease in the overall AI during the clinical study as compared with previous studies conducted with other ventilators. Finally, an AI > 10% in our clinical study was mainly related to a high incidence of auto-triggering, which reflects the ventilator's ability to manage leaks rather than the relevance of the settings chosen by the clinician.

As with ICU ventilators, our bench evaluation also showed very uneven performances of transport ventilators and their NIV algorithms in the presence of leaks. Such heterogeneity has also been previously reported with transport ventilators assessed in invasive conditions.[21,22]

On the whole, our results suggest that rather than being considered as belonging to a group of ventilators, each ICU and transport ventilator should be examined individually regarding its ability to manage NIV conditions. By contrast, dedicated NIV ventilators exhibited more homogeneous behavior during our bench evaluation, with an ability to avoid auto-triggering or delayed cycling while keeping a short

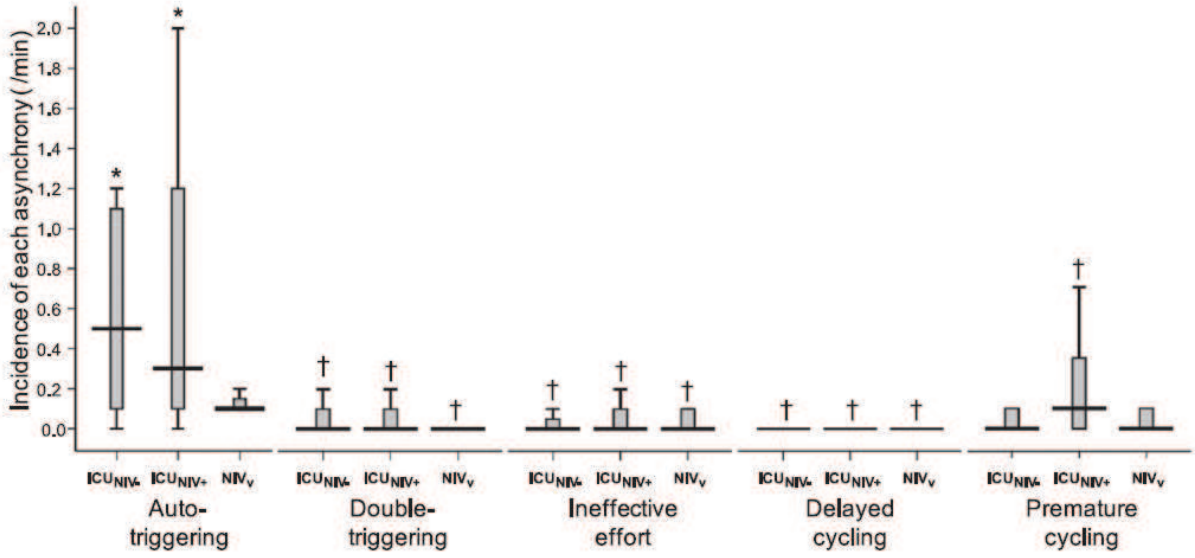

FIGURE 6. Clinical study incidence of each patient-ventilator asynchrony during the three NIV sessions. Each patient-ventilator asynchrony is represented as box plots (thick horizontal bar: median; extremities of the boxes: 25th and 75th percentiles; thin horizontal bars: fifth and 95th percentiles) for each 20-min NIV session: ICU_{NIV-}, ICU_{NIV+}, and NIV_V. *$P < .05$ vs NIV_V, †$P < .05$ vs auto-triggering. See Figure 1 and 5 legends for expansion of abbreviations.

triggering delay despite the presence of leaks. This is consistent with two previous bench studies that showed a better synchronization ability of a dedicated NIV ventilator as compared with several ICU ventilators without[15] or with[13] their NIV algorithm engaged. Our clinical study is the first to our knowledge to confirm that the use of a NIV ventilator to perform NIV in critically ill patients led to a significant decrease in the incidence of patient-ventilator asynchrony.

Limitations

Several limitations of this study should be underlined. First, during the bench study, only mild obstructive respiratory mechanics were simulated, as respiratory mechanics are known to affect the cycling delay. Our aim was to uncover delayed cycling in the presence of inspiratory leaks, which could be minimized in the case of restrictive respiratory mechanics.[12] In addition, COPD represents the most recognized indication for NIV in ICU.[23] Second, only one level of both inspiratory and expiratory leaks was designed. These experimental conditions may not reproduce what happens in clinical conditions. However, our clinical study showed that our bench model succeeded in capturing the kind of asynchronies that may occur in the presence of leaks with each ventilator in the clinical setting.

Clinical Relevance

It is currently unknown if patient-ventilator asynchronies, especially those due to leaks, can affect the clinical outcome of NIV and therefore influence ventilator choice by clinicians. However, several arguments favor the best possible synchronization during NIV. First, it seems reasonable to assume that auto-triggering and delayed cycling will reduce the tolerance of the procedure, an important key to NIV success.[24,25] Second, the occurrence of delayed cycling

Table 3—*Clinical Study Patients Presenting Each Type of Asynchrony With a High Incidence (> 1/min) or an Asynchrony Index > 10%*

Type of Asynchrony	ICUniv−	ICUniv+	NIVv	*P* Value
Auto-triggering	5 (33)	5 (33)	0	.016
Double-triggering	0	1 (7)	0	…
Ineffective effort	0	0	0	…
Delayed cycling	0	0	0	…
Premature cycling	3 (20)	1 (7)	0	.097
At least one asynchrony	6 (40)	5 (33)	0	.012
Asynchrony index > 10%	4 (27)	2 (13)	0	.091

Data are presented as No. (%). See Table 1 and 2 legends for expansion of abbreviations.

can lead to dynamic hyperinflation and contribute to the development of ineffective efforts,[6,19] which are associated with a prolongation of the ventilation during invasive mechanical ventilation.[26] Given the benefits of NIV when avoiding intubation,[23,25,27,28] each factor potentially involved in its success should logically be promoted. However, if no patient exhibited a high incidence of asynchrony with the NIV ventilator in our study, just a few had an AI > 10% with ICU ventilators. We cannot know to what extent this difference may be clinically relevant and further clinical studies addressing the impact of different devices on the outcome of different groups of patients under NIV are needed to formulate some recommendations.

Conclusion

In conclusion, our study shows that dedicated NIV ventilators allow a better patient-ventilator synchrony in the presence of leaks than ICU and transport ventilators, even if their NIV algorithm is engaged, especially for what concerns auto-triggering. When using an ICU or transport ventilator to perform NIV, the NIV algorithm usually improves, at least slightly and with variations among ventilators, triggering and/or cycling synchronization.

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Ms Vignaux: contributed to the study design, patient enrollment, and data collection, and read and approved the final manuscript.
Dr Jolliet: contributed to the study design and patient enrollment, and read and approved the final manuscript.
Dr Thille: contributed to the study design, data analysis, data interpretation, and manuscript preparation, and read and approved the final manuscript.
Dr Richard: contributed to reading and approving the final manuscript.
Dr Brochard: contributed to the study design, data analysis, data interpretation, and manuscript preparation, and read and approved the final manuscript.
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Additional information: The e-Appendix and e-Figures can be found in the "Supplemental Materials" area of the online article.

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CHEST Online Supplement

Patient-Ventilator Asynchrony During Noninvasive Ventilation

A Bench and Clinical Study

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METHODS

Bench study

Ventilators

We have assessed 19 ventilators (Table 1): Eight ICU ventilators, five transport ventilators, and six dedicated NIV ventilators. For each ventilator, the last version available by the time of the manuscript submission has been tested.

Lung Model

A lung simulator, comprising an active lung model Active Servo Lung 5000 (ASL 5000; Ingmar Medical, Pittsburgh, Pennsylvania) and a microprocessor, was used. The microprocessor was programmed with a script driver, using a mathematical model of the equation of motion of the respiratory system, to control the piston's movement in ASL 5000. The script driver was settled with a compliance of 80 ml/cm H_2O and a resistance of 10 cm $H_2O/l.s^{-1}$. The flow profile at the Y piece was 30 L/min. Respiratory rate and inspiratory time were 15 cycles/min and 0.8 s respectively.

Leak System

Three leak conditions have been designed: absence of leak, continuous leak (in order to reveal triggering asynchronies), and inspiratory leak (in order to reveal cycling-off asynchronies). Each ventilator was connected to the ASL 5000 with the manufacturer's circuit if provided, or a standard double-circuit (Intersurgical, Berkshire, UK). To create a calibrated leak we used a T-piece placed between the ASL 5000 and the ventilator circuit. The inspiratory leak was generated by connecting the free extremity of the T-piece to a tube immersed in a 7 cm water column (Fig. 1). In this situation, the leak occurred during the insufflation only when the pressure in the circuit exceeded 7 cm H_2O. For the generation of a continuous leak, the same system was used without water in the

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receptacle, allowing leaks to occur during the whole respiratory cycle. Using this experimental design, the inspiratory leak was characterized by a non-linear relationship of flow varying from 0 to 22 l/min when the pressure rose from 7 to 15 cm H_2O, while the expiratory leak during continuous leak was characterized by a flow of 16 l/min at 5 cm H_2O.

Ventilator setting

Ventilators were set in Pressure Support Ventilation mode, with a Pressure Support Level at 15 cm H_2O and a PEEP at 5 cmH_2O. The pressurization slope was set at the fastest value without overshooting. Inspiratory trigger, when adjustable, was set at the highest sensitivity while avoiding auto-triggering in the case of no leak and was maintained in an identical fashion during leaks. Expiratory trigger was adjusted at 25% of peak inspiratory flow when NIV algorithms were turned off on ICU and transport ventilators, and at 40% of peak inspiratory flow, otherwise automatic, when NIV algorithms were turned on. Some of the NIV ventilators can be used with a passive or active exhalation port. They were tested using the passive exhalation port. Maximal inspiratory time was set, when adjustable, at 3 seconds when assessing the ventilator cycling off synchronization (during inspiratory leak) and at 1 second when assessing the ventilator triggering synchronization (during continuous leak).

Measured Parameters

Each ventilator was assessed in each leak condition for two minutes after steady state. ICU and transport ventilators were tested twice: with and without their NIV algorithm engaged, except the Elisee 250 whose NIV algorithm cannot be turned off. Data were acquired at 512 Hz from the ASL 5000 and stored in a laptop computer for subsequent analysis (Acqknowledge 3.7.3, Biopac Systems, Goleta, CA, USA).

The measured parameters were defined as follows:

- The triggering delay (TD, ms) was the time from the beginning of the simulated inspiratory effort to the beginning of the ventilator's pressurization.
- The *triggering pressure-time product* (PTP_{Trig}, $cmH_2O.s$) was the area under the pressure-time curve from the onset of the simulated inspiratory effort to the return to pressure baseline.
- The *pressure-time product at 300 ms* (PTP_{300}, $cmH_2O.s$) was the area under the pressure-time curve during the first 300 ms after the onset of the inspiratory effort.
- The auto-triggerings were ventilator's insufflations without any previous simulated effort. They are reported as a percentage calculated as follows: Auto-triggering incidence (%) = (Auto-triggered cycles / total ventilator cycles) x 100.

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- Cycling (or expiratory trigger) synchronization was assessed by determining ventilator insufflation time in excess (Ti_{excess}), expressed as a percentage and calculated as follows: $Ti_{excess} = [(Ti_{vent} - Ti_{sim})/ Ti_{sim}] \times 100$, where Ti_{vent} is the time between the beginning of the simulated inspiratory effort and the end of the ventilator's insufflation, and Ti_{sim} the simulated inspiration time. A "delayed cycling" was defined by a $Ti_{vent} \geq 2\ Ti_{sim}$. A "premature cycling" was defined by a $Ti_{vent} < 2/3\ Ti_{sim}$.

Clinical Study

***Study population*:**

The clinical study was conducted in two university hospital ICUs: one medical (Créteil, France), and one medical-surgical (Geneva, Switzerland).

ICU patients requiring NIV for the following indications were eligible:

1) Hypercapnic or non-hypercapnic respiratory failure, defined by at least two of the following[1-2]:
   a. Worsening dyspnoea over the last 10 days in patients with chronic respiratory failure;
   b. Respiratory rate > 25/min;
   c. Arterial pH < 7.35;
   d. $PaCO_2$ > 50 mm Hg;
   e. PaO_2 < 50 mm Hg.
2) To avert extubation failure in patients at risk, i.e. with one of these criteria at the time of extubation[3]:
   a. More than one failure of a weaning trial;
   b. Congestive heart failure;
   c. $PaCO_2$ > 45 mm Hg;
   d. Ineffective cough;
   e. Upper airways stridor at extubation not requiring immediate reintubation.

Non inclusion criteria were classical contraindications to NIV.

Furthermore, patients were included only if either a diaphragmatic (EMGd) or an inspiratory neck muscles (EMGn) surface electromyogram was available and of sufficient quality. Six patients have been excluded due to non reliable EMG signals.

The sample size was arbitrarily set at 15 patients.

Additional settings information

The expiratory trigger was not adjustable on the NIV ventilator because it was automatically adjusted by the ventilator. It was set by default at 25% of the peak inspiratory flow and was not adjustable in the 11 patients with an Evita 4 or XL (Drager). For the remaining four patients with an Engstrom Carestation (GE Healthcare), it was set at 40% for three of them, and 25 % for the other one.

Measurements

Patients received in a random order three consecutive 20 minutes-sessions of NIV: 1) use of an ICU ventilator whose NIV algorithm has been turned off (ICU_{NIV-}), 2) use of an ICU ventilator whose NIV algorithm has been turned on (ICU_{NIV+}) and 3) use of a dedicated NIV ventilator (NIV_V).

Flow was measured with a non-heated pneumotachograph (Fleish No. 2, Lausanne, Switzerland) inserted between the mask and the Y-piece of the circuit and connected to a differential pressure transducer (Validyne MP45, ± 2cmH_2O, Northridge, CA, USA). Volume was obtained by integration of the flow signal. The leak around the mask was quantified as the difference between inspiratory and expiratory volumes. Airway pressure was measured with a differential pressure transducer (Validyne MP45, ± 70cmH_2O, Northridge, CA, USA) placed between the mask and the pneumotachograph. Signals were acquired online over the three NIV sessions (ICU_{NIV-}, ICU_{NIV+}, NIV_V) using an analog-digital converter (MP 100; Biopac systems, Goleta, CA, USA) sampled at 200 Hz, and stored in a laptop computer for subsequent analysis with the Acqknowledge 3.7.3 software (Biopac systems, Goleta, CA, USA). EMGd was recorded with two surface electrodes placed bilaterally over the costal margin, one reference electrode being placed over the sternum[4]. EMGn was recorded with two surface electrodes placed in the posterior triangle of the neck (aiming at recording mainly scalene EMG activity) or over the body of the sternocleidomastoid (aiming at recording mainly sternocleidomastoid activity), one reference electrode being placed over the sternum. The analogue signal was first filtered and digitized at a sampling rate of 1000 Hz by using a Biopac EMG module (Biopac systems, Goleta, CA, USA), then rectified and stored in a laptop computer for subsequent analysis (Acqknowledge 3.7.3; Biopac systems, Goleta, CA, USA).

Respiratory parameters were defined by analyzing these tracings as previously described[1-2]. For each parameter, a mean value of 10 consecutive cycles at 5, 10, 15 and 20 minutes of each NIV session was calculated.

The patient's neural inspiratory time (Ti_p) was measured as the interval between the initial increase in and the initial rapid decrease of electrical activity on the processed EMG signal[1-2, 5]. The difference between the end of Ti_p and the end of the ventilator's pressurization was measured as Ti_{excess}, expressed as a percentage of the Tip as follow: $Ti_{excess} = [(Ti_{vent} - Ti_p)/ Ti_p] \times 100$, where Ti_{vent} is the time between the beginning of the inspiratory effort and the end of the

ventilator's insufflation. Major patient-ventilator asynchronies were defined and detected by visual inspection of the recordings as previously published[1-2, 6]:

Auto-triggering: a cycle delivered by the ventilator without a prior inspiratory EMG activity.

Double-triggering: two cycles separated by a very short expiratory time during the same inspiratory EMG activity.

Ineffective effort: presence of an inspiratory EMG activity not followed by an assisted cycle.

"Delayed cycling": a cycle where the ventilator's insufflation time is greater than twice the Ti_p.

"Premature cycling": a cycle where the ventilator's insufflation ended before the 2/3 of the Ti_p.

Each asynchrony event was considered as frequent if it occurred at an average of > 1/min over the 20 min recording period. A global asynchrony index (AI) was computed as previously published[1-2, 6], defined as the total number of the above events divided by the total number of triggered and non-triggered ventilator cycles. Therefore AI (%) = [number of events / (ineffective triggerings + ventilator cycles)] x 100.

Statistics

Statistical analyses were performed with Statistical Package for the Social Sciences (version 16.0, SPSS, Chicago, IL, USA). Continuous data are expressed as the median (25^{th}-75^{th} percentile). In both the bench and clinical study, the variables did not display a normal distribution, so only non parametric tests were used. A p value of less than 0.05 was considered statistically significant.

Continuous data from the test lung to assess the impact of leaks or NIV algorithm for each kind of ventilator were compared using a Wilcoxon test. Comparisons between different kinds of ventilators were made using a Kruskal-Wallis test then a Mann Whitney test for pairwise comparisons.

Continuous data between the three NIV sessions were compared using a Friedman test, then a Wilcoxon test for paired measures. Comparisons of the proportions of asynchronies between the three sessions were performed with the Cochran Q test, then a Mc Nemar test for pairwise comparisons.

ADDITIONAL RESULTS

Bench Study

Triggering pressure-time product (e-Figure 1)

ICU and transport ventilators with their NIV algorithm turned off in the absence of leaks exhibited a triggering pressure-time product (PTP_{Trig}) of -0.06 (-0.09--0.05) and -0.08 $cmH_2O.s$ (-0.16--0.06) respectively.

With inspiratory leaks, turning on the NIV algorithm led to either an improvement (Engstrom, G5, PB840) or no significant modification (Avea, Evita XL, Servo-i, V500, Vela) of the PTP_{Trig} with ICU ventilators, and to either an

improvement (T1) or a worsening (Medumat, Oxylog 3000, Supportair) of the PTP_{Trig} with transport ventilators. In this last condition, the PTP_{Trig} was -0.06 $cmH_2O.s$ (-0.08--0.04) with ICU ventilators, -0.10 $cmH_2O.s$ (-0.37--0.07) with transport ventilators, and -0.04 $cmH_2O.s$ (-0.06--0.02) with dedicated NIV ventilators. When NIV algorithms were used in the presence of leaks, three ICU ventilators (Avea, Engstrom, PB840), four dedicated NIV ventilators (BiPAP Vision, Trilogy 100, V60, VPAP 4), and one transport ventilator (Elisee 250) exhibited a PTP_{Trig} less than -0.06 $cmH_2O.s$, i.e., the median PTP_{Trig} of ICU ventilators in the absence of leaks (NIV algorithm turned off).

Pressure-time product at 300 ms (e-Figure 2)

In the absence of leaks, all ICU and transport ventilators without their NIV algorithm engaged exhibited a positive PTP_{300} except the Oxylog 3000. Thus, the median PTP_{300} was 1.6 $cmH_2O.ms$ (1.3-1.8) with ICU ventilators. The addition of inspiratory leaks led to a significant decrease in PTP_{300} for all ICU and transport ventilators except one (T1). With the NIV algorithm, the PTP_{300} remained lower than without leaks with all ICU and transport ventilators except three (Engstrom, PB840 and T1), and was even negative for two transport ventilators (Medumat, Oxylog 3000). With both inspiratory leaks and NIV algorithms, the PTP_{300} with ICU, transport and dedicated NIV ventilator was 1.4 (1.3-1.4), 0.3 (-0.2-0.9) and 0.5 $cmH_2O.ms$ (0.3-0.7) respectively. One dedicated NIV ventilator exhibited a negative PTP_{300} (VIVO 40).

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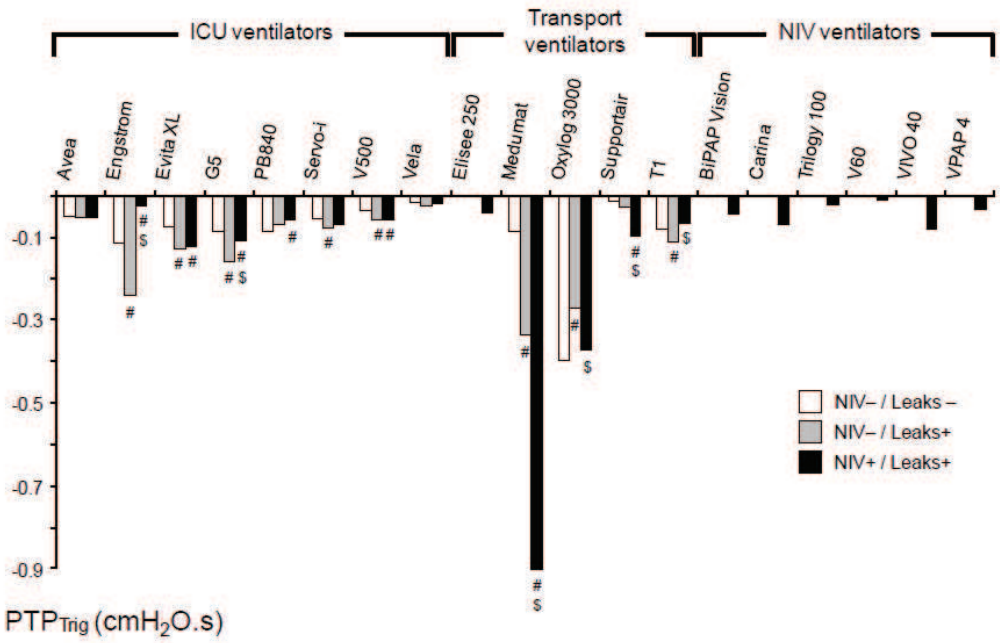
e-Figure 1.



e-Figure 1. *Bench Study* – **Triggering Pressure Time Product (PTP_{Trig}):** Representation of the PTP_{Trig} for ICU and transport ventilators with their NIV algorithm turned off in the absence of any leak (**NIV-/Leaks-**, white bars), then in the presence of inspiratory leaks (**NIV-/Leaks+**, grey bars); and for ICU and transport ventilators with their NIV algorithm turned on as well as for NIV ventilators in the presence of inspiratory leaks (**NIV+/Leaks+**, black bars). #: $p<0.05$ versus NIV-/Leaks-. $: $p<0.05$ versus NIV-/Leaks+.

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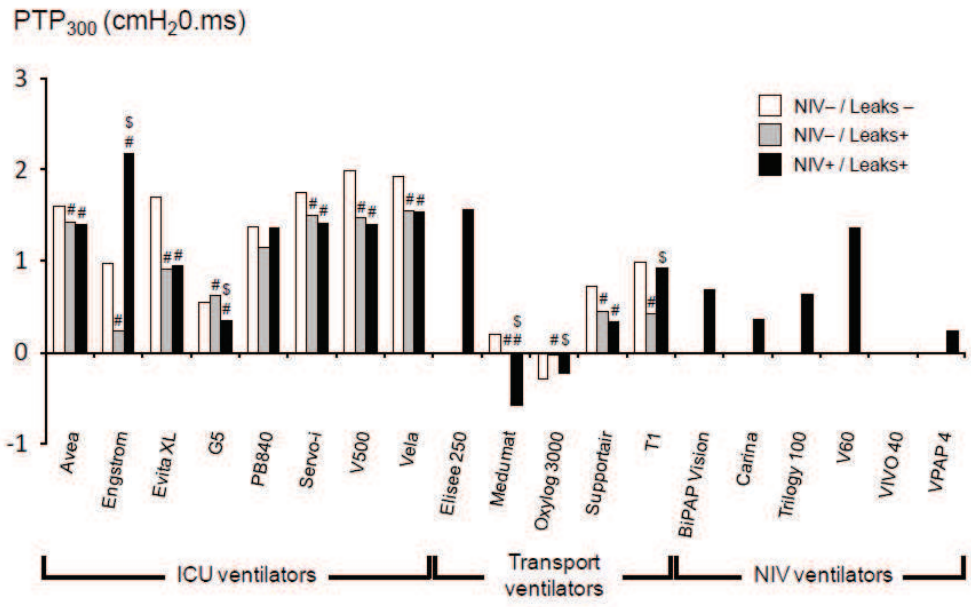
e-Figure 2.



e-Figure 2. *Bench Study* – **Pressure Time Product at 300 ms (PTP_{300})**: Representation of the PTP_{300} for ICU and transport ventilators with their NIV algorithm turned off in the absence of any leak (**NIV-/Leaks-**, white bars), then in the presence of inspiratory leaks (**NIV-/Leaks+**, grey bars); and for ICU and transport ventilators with their NIV algorithm turned on as well as for NIV ventilators in the presence of inspiratory leaks (**NIV+/Leaks+**, black bars). #: $p<0.05$ versus NIV-/Leaks-. $: $p<0.05$ versus NIV-/Leaks+.

6. DISCUSSION GENERALE

6.1. Optimisation des interactions patient-ventilateur en ventilation invasive : intérêt des modes proportionnels

Du fait même de leur principe de fonctionnement, les modes proportionnels améliorent les interactions patient-ventilateur en comparaison aux modes de ventilation assistée traditionnels. En effet, la synchronisation patient-ventilateur est excellente, la variabilité respiratoire respectée, et le volume courant est en quelque sorte choisi par le patient, et ce quel que soit le niveau d'assistance (dans des zones d'assistance « raisonnable »). Dans ces conditions, ajuster le niveau d'assistance d'un mode proportionnel dans le but de cibler une zone d'effort respiratoire normale constitue théoriquement le moyen de perfectionner les interactions patient-ventilateur en ventilation assistée.

En PAV+ nous avons recalculé au lit du malade la pression musculaire générée par les muscles respiratoires du patient et ainsi réajusté le niveau de gain afin de maintenir l'effort respiratoire dans une zone cible. Nous avons montré qu'un tel ajustement était simple à réaliser en routine et la plupart du temps suffisant pour ventiler les patients depuis le début de la ventilation assistée jusqu'à l'extubation. Il s'agit ainsi de la première étude dans l'histoire de la ventilation assistée où le niveau d'assistance a pu être personnalisé en fonction de l'effort respiratoire du patient. Outre le rationnel physiologique fort d'un tel réglage, nous avons par ailleurs observé qu'il s'associait à des valeurs de volume courant et de fréquence respiratoire généralement désirées en pratique clinique. En effet, le volume courant médian était de 6.8 (6.1-8.0) ml/kg de poids prédit et la fréquence respiratoire de 26 (24-30) cycles/min, avec un coefficient de variation d'environ 20% pour chacun de ces paramètres. Enfin, notre étude rapportait pour la première fois la faisabilité d'utiliser le mode PAV+

depuis l'initiation de la ventilation assistée jusqu'à l'extubation. Certaines limites théoriques à l'utilisation de ce mode et des réglages que nous avons proposés méritent cependant être soulignées. Premièrement, en cas de PEP intrinsèque élevée, la mesure le la pression musculaire du patient à partir de la valeur de la pression des voies aériennes sous-estime la pression musculaire réelle et peut théoriquement conduire à un réglage erroné du gain en utilisant notre algorithme. Cependant, en PAV+ le risque de survenue d'une telle PEP intrinsèque élevée est relativement faible car : le volume courant est « choisi » par le patient cycle à cycle et n'augmente pas significativement avec le niveau d'assistance (46, 71); le temps d'insufflation reste très proche du temps inspiratoire neural du patient limitant la possibilité de générer une hyperinflation dynamique (46, 71). De plus, Appendini et coll. ont montré que l'addition d'une PEP externe réduisait considérablement la PEP intrinsèque en PAV chez des patients obstructifs ayant un niveau basal de PEP intrinsèque élevée (101). Une deuxième limite potentielle à l'utilisation de la PAV+ concerne les patients dont l'effort respiratoire est indépendant de la charge imposée au système respiratoire, en cas d'acidose métabolique par exemple ou encore chez certains patients cérébro-lésés. Dans notre étude, le seul patient qui n'avait pas toléré le mode PAV+ présentait justement une acidose métabolique, avec un pic de pression musculaire qui restait supérieur à 10 cm H_2O indépendamment du niveau d'assistance réglé. Enfin, le niveau d'effort respiratoire désirable peut être difficile à apprécier de manière individuelle, en particulier chez les patients présentant une neuro-myopathie sévère. En dehors de ces limites, les réglages simples que nous avons proposés, basés sur l'estimation de la pression musculaire du patient, perfectionnent sur le plan théorique physiologique les interactions patient-ventilateur en ventilation assistée. Leur éventuelle supériorité clinique sur la conduite habituelle du sevrage de la ventilation mécanique en mode VSAI reste cependant à démontrer.

En NAVA, la pression dans les voies aériennes n'est pas directement proportionnelle à la pression musculaire mais à l'activité électrique du diaphragme. Or, le rapport de proportionnalité entre *Pmus* et *EAdi* est variable d'un patient à l'autre, rendant impossible l'ajustement du niveau de NAVA sur la seule valeur de l'*EAdi*. Bellani et coll. ont récemment décrit une méthode permettant de mesurer ce rapport de proportionnalité et donc de recalculer au lit du malade la valeur de la *Pmus* à partir de celle de l'*EAdi* (89). Ce rapport de proportionnalité, bien que variable d'un patient à l'autre, était rapporté comme stable chez un même patient sur une fourchette étroite de niveaux de NAVA. Ces données suggéraient qu'il était donc possible de réajuster le niveau de NAVA de la même manière que le gain en PAV+ au cours de notre étude précédente, c'est-à-dire en fonction de la valeur de la pression musculaire générée par les muscles respiratoires du patient, recalculée à partir de la valeur de l'*EAdi* qui est monitorée sur l'écran du ventilateur. La mesure du rapport de proportionnalité entre *Pmus* et *EAdi* nécessitait cependant la réalisation d'une manœuvre d'occlusion qui peut être inconfortable pour le patient, surtout si elle doit être répétée. Or, l'évolution du couplage neuromusculaire au cours du temps est inconnue. De plus, la valeur du rapport *Pmus*/*EAdi* dépend pour partie de celle de l'*EAdi*, qui dépend elle-même de la position du cathéter *EAdi* ainsi que de l'intégrité des électrodes (76), rendant au final peu probable sa stabilité dans le temps. Enfin, nos données sur une gamme beaucoup plus large de niveaux de NAVA ne confirment pas sa constance en fonction du niveau d'assistance mais retrouvent une relation curvilinéaire entre l'*EAdi* et la *Pmus* selon le niveau de NAVA. L'ajustement du niveau d'assistance en fonction de l'effort respiratoire du patient est donc moins évident en NAVA et reste un objet de recherche. Nos données apportent des informations précieuses à la poursuite des explorations dans ce domaine. Il s'agit de la seule étude comparant une titration de NAVA à une titration de VSAI basée sur l'analyse des indices d'effort respiratoire. Cette analyse nous a permis de mieux définir les bornes d'utilisations de la NAVA. En effet, en

terme d'assistance, les niveaux de NAVA allant de 0.5 à 2.5 cm $H_2O.\mu volt^{-1}$ étaient équivalents à des niveaux d'aide inspiratoire allant de 7 à 25 cm H_2O. Il est à noter que cette fourchette d'utilisation est particulièrement large car le niveau d'aide inspiratoire dépasse rarement 20 cm H_2O en pratique clinique (106). Ainsi, alors que le niveau de NAVA est ajustable sur le ventilateur de 0.1 en 0.1 cm $H_2O.\mu volt^{-1}$ jusqu'à une valeur de 30 cm $H_2O.\mu volt^{-1}$, la gamme d'utilisation semble être majoritairement entre 0.5 et 2 cm $H_2O.\mu volt^{-1}$, et des signes de sur-assistance surviennent fréquemment au-delà de 3-4 cm $H_2O.\mu volt^{-1}$. Chez nos patients, un effort inspiratoire normal, jugé sur la valeur du *PTPes* (27, 37), était ainsi obtenu pour un niveau de NAVA d'environ 1.5 cm $H_2O.\mu volt^{-1}$. En NAVA les expériences d'utilisation clinique sont à ce jour encore plus limitées qu'en PAV+ (107, 108), et de la même manière, les patients qui ont une commande respiratoire principalement indépendante de la charge imposée au système respiratoire (acidose métabolique, patient cérébro-lésé) ne sont probablement pas de bons candidats à la ventilation en NAVA. En revanche, la PEP intrinsèque modifie peu le fonctionnement de la NAVA du fait du neuro-asservissement de la ventilation. Cet avantage est au prix de contraintes techniques liées à l'utilisation du cathéter *EAdi*. Au total, malgré ses avantages physiologiques, l'intérêt clinique de la NAVA en comparaison aux modes de ventilation assistée traditionnels reste à évaluer. Par ailleurs, l'ajustement individuel du niveau de NAVA demeure un objet de recherche.

6.2. Optimisation des interactions patient-ventilateur en ventilation non-invasive : intérêt des algorithmes VNI et ventilateurs dédiés

Au cours de la VNI, la qualité des interactions patient-ventilateur dépend en grande partie de la capacité technologique du ventilateur et des algorithmes qu'il utilise à fonctionner malgré la présence de fuites. En effet, le débit de fuites autour du masque est de nature à

perturber considérablement le signal de débit des voies aériennes utilisé par le ventilateur pour synchroniser son assistance aux efforts inspiratoires du patient. Les algorithmes VNI ont été implémentés dans les ventilateurs de réanimation afin d'améliorer leur comportement en présence de fuites, et les ventilateurs dédiés à la VNI ont été conçus pour ne fonctionner qu'en conditions non-invasives.

Nos deux études mettent en évidence l'ampleur de l'impact potentiel des algorithmes utilisés par le ventilateur en présence de fuite sur la synchronisation patient-ventilateur. Elles ont ainsi permis de pointer la grande hétérogénéité des performances de synchronisation patient-ventilateur des algorithmes VNI selon le ventilateur de réanimation considéré. Cependant, nos données plaident globalement en faveur de l'activation systématique de l'algorithme VNI lors de la réalisation de la VNI avec un ventilateur de réanimation. Notre deuxième travail mettait en évidence la supériorité actuelle de ventilateurs dédiés à la VNI dans l'optimisation des interactions patient-ventilateur en VNI en comparaison aux ventilateurs de réanimation, même lorsque leur algorithme VNI était activé. Dans le même temps, la qualité de la pressurisation de ces ventilateurs dédiés à la VNI était comparable à celle des ventilateurs de réanimation. Cette étude avait l'originalité de combiner une évaluation sur banc d'essai à une évaluation physiologique chez des patients. Notre modèle sur banc d'essai est ainsi le seul rapporté dans la littérature dont la pertinence clinique a été validée expérimentalement.

L'intérêt clinique d'optimiser la synchronisation patient-ventilateur en VNI n'est pas démontré. Il est cependant raisonnable de suspecter que les asynchronies liées aux fuites génèrent un certain inconfort et puissent altérer la tolérance du patient, qui est un facteur clé du succès de la technique (109, 110). Ainsi, étant donné les bénéfices de la VNI lorsqu'elle

permet de sursoir à l'intubation (110-114), il semble licite de promouvoir chaque facteur potentiellement impliqué dans son succès. A ce titre, d'autres options peuvent être considérées, en particulier l'utilisation de modes proportionnels. La PAV+ est cependant probablement inutilisable en aigu en VNI car l'assistance étant proportionnelle aux volumes et débits instantanés, tout débit de fuite perturberait complètement le fonctionnement du mode ainsi que la fiabilité des mesures d'occlusion. En revanche, la NAVA a été évaluée en VNI au cours d'études physiologiques qui ont rapporté une amélioration de la synchronisation patient-ventilateur au cours de son utilisation (85, 87, 88). Cependant, le comparateur était l'algorithme VNI du ventilateur Servo-i (Maquet Critical Care, Solna, Suède), qui n'est pas l'algorithme le plus performant sur banc d'essai (115) et aucune comparaison n'est disponible avec les ventilateurs dédiés à la VNI avec lesquels les asynchronies étaient particulièrement rares dans notre étude. Enfin, la NAVA nécessitant l'introduction du cathéter *EAdi* pour fonctionner, son utilisation semble peu appropriée à la prise en charge d'un patient en détresse respiratoire aiguë, et fait perdre à la VNI une partie de son caractère « non invasif ». Ainsi, parmi les algorithmes de ventilation récemment développés et les solutions technologiques qui les accompagnent, les ventilateurs dédiés à la VNI sont ceux qui optimisent le mieux les interactions patients-ventilateur au cours de la VNI. Il est néanmoins important à l'avenir d'évaluer les éventuels effets cliniques d'une telle optimisation des interactions patient-ventilateur en VNI.

7. PERPECTIVES

7.1. Intérêt physiologique des modes proportionnels en ventilation invasive

En VSAI, l'augmentation de la pression d'aide inspiratoire s'accompagne d'une augmentation de l'incidence de survenue d'efforts inefficaces du fait de la genèse d'une hyperinflation dynamique telle que détaillée au chapitre 1.2.2 (1, 3, 5, 22, 46, 51-55, 57, 60-62). Les efforts inefficaces sont donc considérés comme le témoin d'une sur-assistance en VSAI. Thille et coll. ont ainsi démontré que la réduction du niveau d'aide inspiratoire chez des patients présentant une incidence élevée d'efforts inefficaces conduisait à leur disparition dans deux tiers des cas (21). La plupart des études physiologiques ayant conclu à une amélioration de la synchronisation patient-ventilateur avec l'utilisation des modes proportionnels comparait en fait des titrations d'assistances (46, 53-55, 70). Elles mettaient ainsi en évidence la survenue – attendue – d'efforts inefficaces avec l'augmentation de l'assistance en VSAI mais pas avec les modes proportionnels. Certaines études utilisaient même des critères de cyclage particulièrement propices à générer une hyperinflation dynamique, comme un trigger expiratoire à 5% chez des patients majoritairement obstructifs (54). Finalement, il aurait peut-être été plus juste de considérer qu'en cas de sur-assistance ou de réglages inappropriés, des efforts inefficaces surviennent en VSAI mais pas avec les modes proportionnels. La supériorité des modes proportionnels en termes d'incidence d'asynchronies patient-ventilateur est moins évidente en cas de réglages appropriés de la VSAI. Dans notre comparaison avec la NAVA, lorsque l'effort respiratoire du patient était dans une zone normale en VSAI l'incidence des efforts inefficaces était très faible. Dans l'étude de Thille et coll. cependant, un tiers des patients présentaient des efforts inefficaces persistants après optimisation des réglages du ventilateur (21). Il serait ainsi intéressant de comparer l'incidence des asynchronies patient-ventilateur entre VSAI et modes proportionnels chez ces

patients présentant des asynchronies « réfractaires », c'est à dire après optimisation des réglages en VSAI.

Un autre champ d'investigation physiologique et clinique des modes proportionnels concerne la réalisation des épreuves de sevrage de la ventilation invasive. Actuellement, elles sont principalement réalisées au moyen d'une pièce en T ou en VSAI avec une aide minimale et une PEP externe réglée à 0 cm H_2O (116). Au cours de notre étude sur la PAV+ nous avions réalisé les épreuves de sevrage selon cette dernière modalité. L'utilisation des modes proportionnels et des informations qui y sont associées – valeur de la pression musculaire et de la mécanique respiratoire en PAV+, valeur de l'EAdi et du couplage neuro-ventilatoire en NAVA par exemple – devraient être évaluées tant dans le diagnostic de sevrabilité que dans l'aide au diagnostic étiologique des échecs de sevrage.

7.2. Intérêt clinique des modes proportionnels en ventilation invasive

Malgré certaines questions qui restent à explorer, il existe d'ores et déjà une accumulation suffisante de données physiologiques plaidant en faveur d'une optimisation des interactions patient-ventilateur avec l'utilisation des modes proportionnels en comparaison à la VSAI pour justifier des essais cliniques randomisés. Des deux modes proportionnels actuellement disponibles, la PAV+ est aujourd'hui le meilleur candidat pour la conduite d'un essai randomisé car nous avons démontré la faisabilité en clinique de réglages optimisant les interactions patient-ventilateur pendant toute la durée de la ventilation assistée. En NAVA, l'ajustement du niveau de NAVA reste un sujet de recherche et la stabilité du mode pendant toute la durée de la ventilation assistée reste à démontrer. Un essai randomisé comparant la PAV+ à la VSAI est ainsi prévu, l'essai PROMIZING, auquel nous participerons. Dans cet essai, les réglages de la PAV+ seront principalement basés sur ceux que nous avions

proposés, ciblant une pression musculaire entre 5 et 10 cm H_2O.

7.3. Intérêt clinique d'optimiser les interactions patient-ventilateur en ventilation non-invasive

Le premier obstacle à l'évaluation clinique de l'impact des asynchronies patient-ventilateur en VNI concerne leur détection. En effet, si la détection des efforts inefficaces en ventilation invasive peut se faire par l'analyse des courbes de débit et de pression des voies aériennes disponibles sur l'écran du ventilateur (61, 117, 118), la détection et la caractérisation des asynchronies liées aux fuites en VNI est en revanche impossible en l'absence d'un signal physiologique d'effort inspiratoire du patient (Fig. 21).

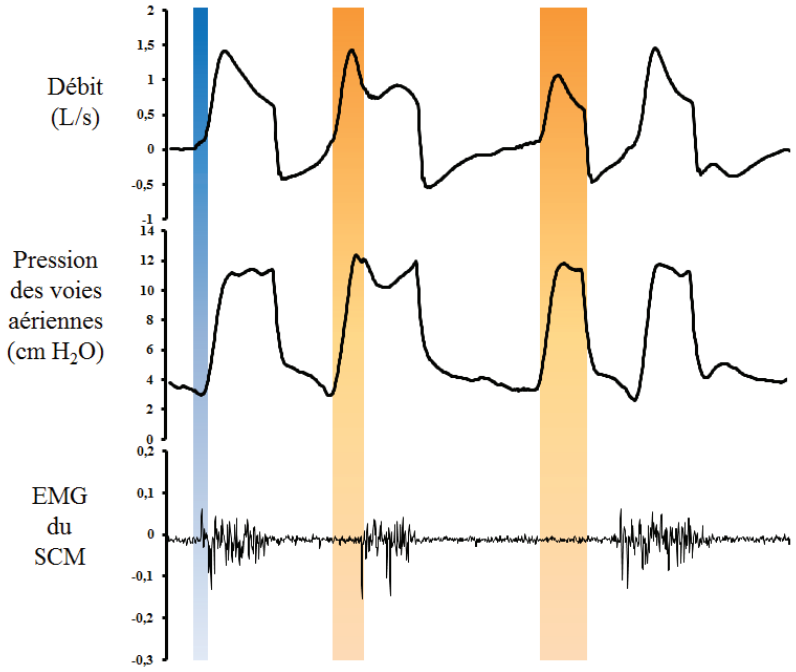


Figure 21 Exemple d'asynchronies en ventilation non-invasive. Les courbes représentent de haut en bas le débit dans les voies aériennes, la pression des voies aériennes, et l'électromyogramme (EMG) du muscle sterno-cléido-mastoïdien (SCM) chez un patient en ventilation non-invasive. Le surlignage bleu pointe un cycle normalement déclenché par un effort inspiratoire du patient. Les surlignages oranges mettent en évidence des auto-déclenchements, dont l'un (le premier) est secondairement « rattrapé » par un effort inspiratoire du patient. Cette caractérisation précise des asynchronies chez un patient sous VNI aurait été impossible par la seule analyse des courbes de débit et de pression des voies aériennes.

Il est donc important de développer de nouveaux moyens de détection de l'effort inspiratoire au lit du malade afin d'évaluer l'éventuel bénéfice clinique d'optimiser la synchronisation patient-ventilateur par l'utilisation d'algorithmes performants. Nous prévoyons un projet en plusieurs étapes visant à évaluer l'échographie diaphragmatique (119, 120) comme outil de détection et de caractérisation des asynchronies patient ventilateur, puis à utiliser ce nouvel outil afin d'évaluer l'efficacité de la VNI en fonction de la qualité de la synchronisation patient-ventilateur.

8. CONCLUSION

En ventilation invasive, personnaliser l'assistance des modes proportionnels dans le but de cibler une zone d'effort respiratoire normale optimise les interactions patient-ventilateur et est réalisable en utilisation clinique avec la PAV+. En VNI, les algorithmes utilisés par les ventilateurs en présence de fuite ont un impact important sur la synchronisation patient-ventilateur. Les ventilateurs dédiés à la VNI améliorent la synchronisation patient-ventilateur plus encore que les algorithmes VNI sur les ventilateurs de réanimation, dont l'efficacité varie grandement selon le ventilateur considéré. L'intérêt clinique de ces optimisations des interactions patient-ventilateur que permettent les nouveaux algorithmes de ventilation devra être évalué au cours d'essais randomisés.

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RESUME

En ventilation assistée, les interactions patient-ventilateur, qui sont associés au pronostic, dépendent pour partie des algorithmes de ventilation.
Objectifs: Caractériser l'intérêt potentiel des nouveaux algorithmes de ventilation dans l'optimisation des interactions patient-ventilateur: 1) en ventilation invasive, deux modes et leurs algorithmes nous ont semblé novateurs et nous avons cherché à personnaliser l'assistance du ventilateur en fonction de l'effort respiratoire du patient au cours de ces modes proportionnels: ventilation assistée proportionnelle (PAV+) et ventilation assistée neurale (NAVA) ; 2) en ventilation non-invasive (VNI) nous avons évalué si les algorithmes VNI des ventilateurs de réanimation et des ventilateurs dédiés à la VNI diminuaient l'incidence des asynchronies patient-ventilateur.
Méthodes : 1) En PAV+ nous avons décrit un moyen de recalculer le pic de pression musculaire réalisée par le patient à chaque inspiration à partir du gain réglé et de la pression des voies aériennes monitorée par le respirateur. Nous avons alors évalué la faisabilité clinique d'ajuster l'assistance en ciblant un intervalle jugé normal de pression musculaire. 2) Nous avons comparé une titration de l'assistance en NAVA et en aide inspiratoire (AI) en se basant sur les indices d'effort respiratoire. 3 et 4) En VNI, nous avons évalué l'incidence des asynchronies patient-ventilateur avec et sans l'utilisation d'algorithmes VNI : sur banc d'essai au cours de conditions expérimentales reproduisant la présence de fuites autour de l'interface ; en clinique chez des patients de réanimation.
Résultats : En PAV+, ajuster le gain dans le but de cibler un effort respiratoire normal était faisable, simple et souvent suffisant pour ventiler les patients depuis le sevrage de la ventilation mécanique jusqu'à l'extubation. En NAVA, l'analyse des indices d'effort respiratoire a permis de préciser les bornes d'utilisation et de comparer les interactions patient-ventilateur avec l'AI dans des intervalles d'assistance semblables. En VNI, nos données pointaient l'hétérogénéité des algorithmes VNI sur les ventilateurs de réanimation et retrouvaient une meilleure synchronisation patient-ventilateur avec l'utilisation de ventilateurs dédiés à la VNI pour des qualités de pressurisation par ailleurs identiques.
Conclusions : En ventilation invasive, personnaliser l'assistance des modes proportionnels optimise les interactions patient-ventilateur et il est possible de cibler une zone d'effort respiratoire normale en PAV+. En VNI, les ventilateurs dédiés améliorent la synchronisation patient-ventilateur plus encore que les algorithmes VNI sur les ventilateurs de réanimation, dont l'efficacité varie grandement selon le ventilateur considéré.

ABSTRACT

During assisted mechanical ventilation, patient-ventilator interactions, which are associated with outcome, partly depend on ventilation algorithms.
Objectives: : 1) during invasive mechanical ventilation, two modes offered real innovations and we wanted to assess whether the assistance could be customized depending on the patient's respiratory effort during proportional ventilatory modes: proportional assist ventilation with load-adjustable gain factors (PAV+) and neurally adjusted ventilator assist (NAVA); 2) during noninvasive ventilation (NIV): to assess whether NIV algorithms implemented on ICU and dedicated NIV ventilators decrease the incidence of patient-ventilator asynchrony.
Methods: 1) In PAV+ we described a way to calculate the muscle pressure value from the values of both the gain adjusted by the clinician and the airway pressure. We then assessed the clinical feasibility of adjusting the gain with the goal of maintaining the muscle pressure within a normal range. 2) We compared titration of assistance between neurally adjusted ventilator assist (NAVA) and pressure support ventilation (PSV) based on respiratory effort indices. During NIV, we assessed the incidence of patient-ventilator asynchrony with and without the use of NIV algorithms: 1) using a bench model; 2) and in the clinical settings.
Results: During PAV+, adjusting the gain with the goal of targeting a normal range of respiratory effort was feasible, simple, and most often sufficient to ventilate patients from the onset of partial ventilatory support until extubation. During NAVA, the analysis of respiratory effort indices allowed us to precise the boundaries within which the NAVA level should be adjusted and to compare patient-ventilator interactions with PSV within similar ranges of assistance. During NIV, our data stressed the heterogeneity of NIV algorithms implemented on ICU ventilators. We therefore reported that dedicated NIV ventilators allowed better patient-ventilator synchronization than ICU ventilators, even with their NIV algorithms engaged.
Conclusions: During invasive mechanical ventilation, customizing the assistance during proportional ventilatory modes with the goal of targeting a normal range of respiratory effort optimizes patient-ventilator interactions and is feasible with PAV+. During NIV, dedicated NIV ventilators allow better patient-ventilator synchrony than ICU ventilators, even with their NIV algorithm engaged. ICU ventilators' NIV algorithms efficiency is however highly variable among ventilators.