Substrats neurophysiologiques des interactions patient-ventilateur et des sensations respiratoires correspondantes

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Pour Virginie, Theo, Nathan, Loane.

Pour mes parents.

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PREAMBULE ET INTRODUCTION

La ventilation contrôlée a pour objectif d'optimiser les échanges gazeux au sein du parenchyme pulmonaire chez des patients dépourvus de toute activité musculaire respiratoire. La totalité du travail respiratoire est alors assurée par le ventilateur (1). Cette ventilation contrôlée peut être opposée à un ventilation dite « assistée » lors de laquelle le patient déclenche son ventilateur voir contribue, dans une proportion variable, à la genèse de sa propre ventilation (1). L'objectif de la ventilation assistée est alors de diminuer le travail des muscles respiratoire du patient tout en préservant l'activité spontanée de ces muscles. Un certain nombre de circonstances implique nécessairement le recours à la ventilation assistée. Ainsi, elle est un état de fait lorsque qu'un patient initialement ventilé de façon contrôlée présente un niveau d'éveil suffisant pour l'autoriser à déclencher son ventilateur. Son utilisation est systématique en ventilation non invasive (VNI) où la vigilance du patient est généralement normale. De plus, un certain nombre d'arguments suggèrent que la préservation d'une activité ventilatoire spontanée pourrait prévenir en partie la survenue d'une dysfonction diaphragmatique induite par la ventilation mécanique (2, 3). Si les arguments justifiant l'utilisation de la ventilation assistée sont assez clairs, son utilisation doit toutefois tenir compte d'une contrainte majeure : assurer une adéquation satisfaisante entre les efforts inspiratoires, voir expiratoires, du patient et l'assistance délivrée par le ventilateur. En d'autres termes, le ventilateur doit délivrer son assistance en harmonie avec l'activité des muscles respiratoires du patient. L'inadéquation entre l'activité des muscles respiratoires du patient et l'assistance délivrée par le ventilateur se traduit par la survenue d'une dysharmonie patient-ventilateur. De récentes données ont souligné les conséquences potentiellement délétères de celle-ci. (4-6). La minimiser en la détectant précocement et en soulageant les

sensations respiratoires qui y sont associées est un des objectifs majeurs de la prise en charge d'un patient en ventilation mécanique.

L'objectif ultime d'étudier les interactions patient-ventilateur est de pouvoir limiter les sensations respiratoires négatives perçues par le patient sous ventilation mécanique. Pour atteindre ces objectifs, des nouveaux modes ventilatoires ont été développés. Regroupés sous le terme de « modes proportionnels », leur principe est de délivrer une assistance proportionnelle à l'effort inspiratoire du patient. A travers ces nouveaux modes ventilatoires, nous étudierons les déterminants des interactions patient-ventilateur, leur impact sur la dysharmonie patient ventilateur, et les moyens de la détecter.

Précédée d'une synthèse des connaissances actuelles, cette thèse expose en quatre chapitres quatre travaux distincts. Trois d'entre eux ont d'ores et déjà fait l'objet d'une publication scientifique (chapitres I, II et IV) et un quatrième est accepté pour publication sous réserve de modifications mineures (chapitre III).

SYNTHESE DES CONNAISSANCES

L'objectif de la présente synthèse est d'exposer les connaissances permettant de comprendre les déterminants de la dysharmonie patient-ventilateur, ainsi que les moyens potentiels de la minimiser. Ce pré-requis est en effet indispensable à la compréhension des travaux scientifiques qui constituent le corps de la présente thèse.

1 Dysharmonie patient-ventilateur

L'interaction patient-ventilateur dépends de trois acteurs: a) la commande ventilatoire centrale ; b) les effecteurs musculaires de cette commande dont le principal est le diaphragme ; c) les charges imposées à l'appareil respiratoire. Trouver le bon équilibre entre ce trio est nécessaire à l'obtention d'une interaction satisfaisante entre le patient et son ventilateur. Une inadéquation entre d'une part l'activité des muscles respiratoires et de la commande centrale et, d'autre part, l'assistance délivrée par le ventilateur se traduit par la survenue d'une dysharmonie patient-ventilateur.

1.1 Acteurs de la dysharmonie patient-ventilateur

1.1.1 Commande ventilatoire centrale

Une des originalités de la ventilation est son double système de commande centrale. En effet, elle possède une commande automatique générée par les centres respiratoires du tronc cérébral, mais aussi une commande adaptative modulée par des structures supra-pontiques. Plusieurs arguments laissent à penser que l'adaptation aux contraintes respiratoires mécaniques, comme en ventilation assistée, implique non pas les structures du tronc cérébral,

mais les structures supra-pontiques. Ainsi, l'activation de plusieurs structures corticales telles que l'aire motrice supplémentaire, le cortex pré-moteur, le cortex cingulaire antérieur et le cortex moteur primaire serait impliquée dans la modulation comportementale et volontaire de la ventilation (7-9). De plus, certaines structures du système limbique, siège des émotions, pourraient jouer également un rôle dans le contrôle comportemental de la ventilation (10, 11). En conséquence, ces structures supra-pontiques sont des acteurs clés de l'interaction patient-ventilateur en ventilation mécanique.

1.1.2 Effecteurs musculaires de la commande centrale

La commande ventilatoire centrale est transmise aux motoneurones de la moelle épinière à destinée des muscles respiratoires par la voie bulbo-spinale pour la commande automatique, et par la voie cortico-spinale pour la commande volontaire. Quelle que soit l'origine de la commande ventilatoire centrale, les effecteurs musculaires de la ventilation sont activés selon une même séquence temporelle qui débute par les muscles dilatateurs des voies aériennes, puis par les muscles « pompes » inspiratoires.

1.1.2.1 Diaphragme

Le principal effecteur musculaire de la commande ventilatoire centrale est le diaphragme, dont les particularités structurelles (composition en fibres, équipement enzymatique, vascularisation) uniques lui autorisent une activité contractile permanente tout au long de la vie. La distribution de la commande aux muscles ventilatoires privilégie les muscles qui possèdent le meilleur rendement ventilatoire mécanique et donc ceux qui contribuent le plus à la genèse du volume courant (V_T). Le diaphragme est le principal de ces muscles. En revanche, en situation de charge, le diaphragme est assisté par d'autres muscles respiratoires qui suivent eux aussi une activation séquentielle : muscles scalènes,

parasternaux, puis sterno-cleido-mastoïdiens. Ces muscles péjorativement qualifiés « d'accessoires » ont en fait un rôle clef. Ils pourraient contribuer à la protection du diaphragme contre des phénomènes de fatigue induits par des situations de charge. A titre d'exemple, plusieurs travaux ont souligné la participation croissante des muscles intercostaux en situation de charge, tandis que la contribution du diaphragme à la genèse du V_T diminuait simultanément (12-14).

1.1.2.2 Muscles inspiratoires extra-diaphragmatique

Ainsi, il est clairement montré que, même si le diaphragme reste le principal muscle inspiratoire, d'autres muscles inspiratoires contribuent à la genèse du volume courant. En plus de leur rôle « protecteur » du diaphragme exposé précédemment, certains auteurs suggèrent que la mesure de l'activité des muscles inspiratoires extra-diaphragmatiques pourraient être plus accessibles et plus informative lorsque le système respiratoire est soumis à une charge ou lorsque le diaphragme est défaillant (13, 15). Parmi ces muscles inspiratoires extra-diaphragmatiques, trois ont plus particulièrement été étudiés. Il s'agit des muscles scalènes, des muscles intercostaux parasternaux et des muscles des ailes du nez ou *Alae nasi*.

Muscles des ailes du nez. Les muscles des ailes du nez ou *Alae nasi* appartiennent à une catégorie particulière de muscles inspiratoires : les dilatateurs des voies aériennes supérieures. Le rôle de ces muscles est de diminuer la résistance des voies aériennes supérieures lors de l'inspiration (16, 17). L'activité des muscles *Alae nasi* semble proportionnelle à la charge imposée à l'appareil respiratoire. Ainsi, chez l'enfant, le battement des ailes du nez, conséquence de l'activation des muscles *Alae nasi*, est un signe élémentaire de détresse respiratoire. Toujours chez l'enfant, l'activation des muscles *Alae nasi* est précoce lors de l'exposition à des charges chimiques (hypercapnie) (18). Dans cette situation l'activité des muscles *Alae nasi* croit proportionnellement à celle du diaphragme

(19). Chez des patients atteints de syndrome des apnées obstructive du sommeil, l'application d'un niveau de pression télé-expiratoire positive suffisant pour supprimer les apnées induit une nette diminution de l'activité éléctromyographique (EMG) d'*Alae nasi* (20).

Scalènes. Les scalènes sont probablement les muscles inspiratoires extra-diaphragmatiques les mieux connus. En respiration calme, leur activité phasique est détectable mais son amplitude est faible, variable d'un sujet à l'autre et variable dans le temps chez un sujet donné (21). En revanche, si des charges sont imposées à l'appareil respiratoire, les muscles scalènes sont recrutés précocement (21). Ainsi, une activité phasique des scalènes est très fréquemment retrouvée chez les patients atteints de pathologies respiratoires chroniques (22). Enfin, chez des sujets sains respirant contre des charges inspiratoires, de même que chez des patients ayant une dysfonction chronique du diaphragme, l'augmentation de l'activité des muscles du cou, laquelle englobe l'activité des scalènes, est associée à un moindre confort respiratoire (23, 24). Ces données suggèrent que l'activité des muscles scalènes, modérée et inconstante en respiration calme, augmente de façon importante lorsque l'appareil respiratoire est soumis à des charges. Réciproquement, dans l'insuffisance respiratoire aiguë, la réduction par la ventilation mécanique de tout ou partie de la charge imposée aux muscles respiratoires s'accompagne d'une diminution de l'activité EMG phasique des muscles du cou (25).

Muscles intercostaux parasternaux. Les muscles intercostaux parasternaux correspondent à la portion de muscles intercostaux internes allant du sternum à la jonction chondrocostale. Il s'agit de muscles inspiratoires dont l'action est synergique de celle des muscles scalènes. Isolément, leur contraction produit une dépression thoracique d'environ 3 cmH_2O (26). Comme pour les muscles scalènes, l'activité EMG des muscles parasternaux est augmentée lors de l'application d'une charge inspiratoire (27) . Elle pourrait

être également un marqueur de sévérité dans la décompensation de broncho-pneumopathie chronique obstructive (13), la mucoviscidose (14) ou encore dans l'asthme instable (28).

Cette relation constante entre charge et activité des muscles inspiratoires extra-diaphragmatiques est particulièrement séduisante dans le contexte de la dysharmonie patient-ventilateur. Minimiser leur activité EMG pourrait être un objectif pour réduire cette dysharmonie.

1.1.3 Charges imposées à l'appareil respiratoire

Le dernier acteur de la dysharmonie patient ventilateur est le niveau de charge imposé à l'appareil respiratoire. Bien que cette charge chimique ou mécanique soit fréquemment le facteur précipitant la mise en route d'une ventilation mécanique, une pathologie respiratoire chronique (syndrome restrictif, BPCO…) ou une complication aiguë de la ventilation mécanique (pneumopathie nosocomiale, pneumothorax, etc…) peuvent elles aussi augmenter la charge imposée à l'appareil respiratoire. Ainsi, la ventilation assistée représente un modèle particulier d'étude de l'adéquation charge-capacité, puisqu'elle « décharge » les muscles de patients dont l'appareil respiratoire était préalablement exposé, du fait d'une pathologie respiratoire aiguë, à un niveau de charge élevé.

1.2 Conséquences d'une dysharmonie patient-ventilateur.

Les conséquences de cette vaste entité qu'est la dysharmonie patient-ventilateur, peuvent être multiples. De récents travaux suggèrent que les asynchronies patient-ventilateur, la dyspnée et l'angoisse pourraient être les premières conséquences d'une dysharmonie patient-ventilateur (4, 5, 29, 30).

1.2.1 Asynchronies patient-ventilateur

Une des premières conséquences visible d'une dysharmonie patient ventilateur est l'éventuelle survenue d'asynchronies patient-ventilateur. La détection de celles ci par l'analyse minutieuse des courbes de pression et de débit requiert une certaine expertise (31). Elle peut être simplifiée par l'une analyse conjointe de l'activité électromyographique du diaphragmae (EAdi) (32, 33).

1.2.1.1 Principales asynchronies

Les asynchronies patient-ventilateur peuvent résulter de deux mécanismes différents. D'une part, un décalage de phase entre l'activité des muscles respiratoires du patient et l'assistance délivrée par le ventilateur. Il existe alors une inadéquation entre les temps inspiratoire et expiratoire du patient et ceux du ventilateur (34, 35). D'autre part, une inadéquation entre le niveau d'assistance fourni par le ventilateur et la demande du patient, laquelle peut alors s'avérer insatisfaite (36). Ces deux mécanismes interagissent, comme nous le verrons par la suite.

La classification la plus simple des asynchronies patient-ventilateur et de leurs mécanismes sous-jacents respectifs repose sur le temps du cycle ventilatoire auquel ces évènements surviennent : déclenchement du ventilateur, pressurisation des voies aériennes, ou transition entre inspiration et expiration. Nous présentons et classons ici la plupart de ces évènements.

Déclenchement du ventilateur.

Les deux principales asynchronies patient-ventilateur survenant lors du déclenchement du ventilateur sont l'appel inefficace et l'autodéclenchement.

Appel inefficace. Il s'agit de l'absence de déclenchement du ventilateur malgré la genèse d'un effort inspiratoire par le patient. Ce type d'évènement est énergétiquement coûteux puisque l'effort musculaire réalisé n'est pas suivi d'une insufflation par le ventilateur. La distension thoracique est le principal facteur favorisant la survenue des appels inefficaces (35, 37).

Autodéclenchement. Il s'agit d'un déclenchement du ventilateur en dehors de tout effort du patient (38, 39). Outre la trop forte sensibilité du trigger, le principal mécanisme impliqué dans la genèse de ce type d'évènement est une distorsion du signal de pression ou de débit, laquelle peut résulter de fuites (40), des battement cardiaques ou de la présence d'eau dans le circuit du ventilateur (38).

Mise en pression des voies aériennes (insufflation)

L'adéquation entre l'offre que représente la mise en pression des voies aériennes par le ventilateur et la demande du patient qui résulte de l'intensité de la commande centrale est un déterminant majeur de l'harmonie patient-ventilateur. Si l'offre ne satisfait pas la demande, il persistera, lors de l'insufflation, une activité des muscles inspiratoires. En ventilation assistée contrôlée (VAC), où la variable dépendante est la pression, la persistance d'une activité musculaire inspiratoire lors de l'insufflation se traduit par une déviation de la courbe de pression comparé à son tracé obtenu lorsque les muscles inspiratoires sont relaxés (41-43). En ventilation spontanée avec aide inspiratoire (VSAI), la variable dépendante est le débit, c'est donc son tracé qu'il conviendra d'étudier (29, 44) pour détecter une asynchronie patient-ventilateur.

Transition entre l'inspiration et l'expiration

La transition entre l'inspiration et l'expiration est le troisième temps du cycle ventilatoire auquel sont susceptibles de survenir des évènements témoignant d'une

dysharmonie patient-ventilateur (45). Du point vue du patient, cette transition est marquée par la diminution puis l'arrêt de l'activité des muscles inspiratoires (à noter qu'il persiste toutefois au cours de l'expiration une minime activité inspiratoire qui est habituellement nommée activité post-inspiratoire (46)) et, parfois, par l'apparition d'une activité musculaire expiratoire (35). Du point de vue du ventilateur, cette même transition se traduit par l'arrêt de l'insufflation et l'ouverture de la valve expiratoire. A ce temps du cycle ventilatoire, l'asynchronie patient-ventilateur peut donc résulter de deux mécanismes : d'une part l'arrêt prématurée de l'insufflation avant la fin de l'inspiration, d'autre part la poursuite de l'insufflation au delà de l'inspiration.

L'arrêt prématuré de l'insufflation alors que persiste une activité des muscles inspiratoires résulte lui-même de mécanismes dont l'expression dépend du mode ventilatoire choisi. Chez les patients ventilés en VAC, l'arrêt prématuré de l'insufflation résulte en général d'un temps inspiratoire trop court ou d'un volume courant trop faible, lesquels n'ont pu satisfaire la « soif d'air » du patient. Cela se traduit sur les courbes de pression et de débit par la visualisation de deux cycles inspiratoires successifs séparé par un temps expiratoire inexistant ou très court. Cette asynchronie est appelée double déclenchement. En revanche, chez les patients ventilés en VSAI, où la grandeur réglée est la pression et la grandeur variable est le débit, la fin prématurée de l'insufflation survient plutôt chez des patients à l'appareil respiratoire trop faiblement compliant, soit du fait d'une diminution de la compliance pulmonaire comme dans les suites immédiates d'un syndrome de détresse respiratoire aiguë, soit du fait d'une diminution de la compliance pariétale ce qui est le cas des patients obèses (29, 47, 48).

La poursuite de l'insufflation au delà de l'inspiration résulte, en VAC, d'un temps inspiratoire trop long. En revanche, en VSAI, l'ouverture retardée de la valve expiratoire est plutôt favorisée par les pathologies associées à un allongement de la constante

de temps (BPCO par exemple), mais aussi par des niveaux d'aide trop élevés et par un seuil expiratoire correspondant à un débit trop faible (49). Enfin, des hauts niveaux de fuites, problème crucial en VNI, peuvent aussi s'avérer responsables d'un allongement majeur de la durée de l'insufflation (50).

1.2.1.2 Impact, conséquences connus

La prévalence des asynchronies patient-ventilateur est mal connue. Pendant longtemps, seules des séries incluant un très faible nombre de patients, souvent moins de 20, étaient disponibles (51). Ces petites séries ne permettaient pas d'évaluer avec précision la prévalence de la dysharmonie patient-ventilateur, mais ont eu le mérite de sensibiliser les cliniciens à l'existence de ce phénomène. Jusqu'à peu, la seule étude réalisée sur une large population (200 patients) avait été conduite chez des patients admis en unité de sevrage longue durée au décours d'un séjour en réanimation (52). Les auteurs retrouvaient une asynchronie au déclenchement du ventilateur chez 11 % des patients, laquelle était plus fréquente chez les patients âgés, atteints de BPCO et présentant une hypercapnie sévère. De façon plus récente ont été publiés les résultats d'une étude de prévalence conduite chez 62 patients hospitalisés en réanimation, ventilés sur sonde d'intubation et aptes à déclencher leur ventilateur (53). La prévalence des asynchronies était évaluée au moyen d'un indice dit d'asynchronie. Cet indice se révélait être supérieur à 10 % chez 24 % des patients. Les appels inefficaces et les doubles déclenchements représentaient respectivement 85 % et 13 % des évènements témoignant d'une dysharmonie patient-ventilateur. Parmi les appels inefficaces, 78 % survenaient lors de la période expiratoire et 7 % au cours de l'inspiration. Les autres évènements témoignant d'une dysharmonie, comme les autodéclenchements, arrêts prématurés de l'insufflation ou insufflations prolongées, représentaient moins de 1 % de la somme des évènements.

En réanimation, la prévalence des asynchronies patient-ventilateur semble donc être élevée, du moins dans des populations sélectionnées par la sévérité de l'atteinte respiratoire. Néanmoins, cette prévalence élevée n'implique par forcément que les asynchronies patient-ventilateur aient un impact sur le pronostic des patients. Si le bon sens conduit à supposer qu'il existe un lien entre harmonie patient-ventilateur et pronostic, rares sont les études ayant documenté l'existence de ce lien. Il semble néanmoins que les patients intubés présentant un taux d'asynchronies patient-ventilateur marqué aient une durée de ventilation mécanique plus élevée et nécessitent plus fréquemment la réalisation d'une trachéotomie (53). Chez des patients trachéotomisés admis en unité de sevrage prolongé, les asynchronies patient-ventilateur étaient de plus associées à un moindre succès du sevrage de la ventilation mécanique (52). Enfin, chez les patients bénéficiant d'une VNI, deux enquêtes multicentriques ont montré que les patients en échec de VNI présentaient des niveaux de fuites plus élevés que les patients chez lesquels la VNI étaient réalisée avec succès (54, 55). De plus, dans ces deux enquêtes, la mauvaise tolérance de la VNI, qui intègre de multiples facteurs incluant les asynchronies patient-ventilateur, était un facteur prédictif indépendant d'échec de la VNI, lequel échec était associé à un allongement de la durée de ventilation mécanique et à une surmortalité (56). Il semble donc bien exister un lien entre les asynchronies patient-ventilateur et le bénéfice qu'est supposé apporter la ventilation mécanique.

De plus, les asynchronies patient-ventilateur semblent largement contribuer aux profondes altération de l'architecture du sommeil dont souffre la majeure partie des patients ventilés en réanimation (57). Ces profondes altérations de l'architecture du sommeil sont maintenant bien démontrées et leurs conséquences délétères sont multiples et bien connues (58-61).

1.2.2 Dyspnée

1.2.2.1 Définition et mécanisme

La dyspnée se définit au mieux comme ”une sensation subjective d’inconfort respiratoire, qui se compose de multiples sensations distinctes en terme qualitatif et quantitatif, sous tendues par des mécanismes différents généralement intriqués, dont l’intensité de l’affect négatif varie indépendamment de l’intensité de la sensation elle-même et qui s’accompagne d’un impact émotionnel et comportemental également variables” (62). Elle résulte d’un déséquilibre entre, d’une part la commande respiratoire centrale provenant du tronc cérébral ou suprapontique et d’autre part la réponse périphérique de l’appareil respiratoire qui active les afférences respiratoire et informe en retour le cerveau de son aptitude à répondre à l’ordre donné. Pour permettre une comparaison entre l’ordre donné par la commande respiratoire centrale et son exécution par l’effecteur (appareil respiratoire), une décharge corollaire, c'est-à-dire une copie de l’information émise à partir des centres respiratoires moteurs, est projetée vers le cortex somesthésique. Ce dernier compare alors l’ordre donné par la commande respiratoire centrale à son exécution « réelle », à savoir la réponse périphérique de l’appareil respiratoire transmise par les afférences respiratoires. Un déséquilibre ou une inadéquation entre les afférences respiratoires et cette décharge corollaire fait immédiatement l’objet d’un traitement cognitivo-affectif négatif et conduit à la sensation de dyspnée.

1.2.2.2 Connaissance en ventilation mécanique

Contrairement à la douleur (63), la dyspnée n’est actuellement pas recherchée en routine en réanimation, à part peut être lors du sevrage de la ventilation mécanique (64-67). Jusqu'à peu, seules cinq études prospectives conduites sur un faible effectif de patients s’étaient intéressées à la dyspnée chez les patients sous assistance ventilatoire mécanique (64,

66, 68-70) (voir infra, Annexe 2). Les premières études réalisés par Knebel et al (64) et Conelly et al (67), chez 21 patients ventilés au cours d'une épreuve de sevrage en aide inspiratoire ou en ventilation synchronisé intermittente, rapportaient une dyspnée fréquente et inversement corrélée à un score d'humeur (71) qui compile des échelles d'anxiété, de dépression, d'humeur, de vitalité, de fatigue et, de confusion (67). De même, en dehors du sevrage ventilatoire, Powers et al (70) objectivaient une dyspnée d'intensité moyenne à sévère chez la moitié des 28 patients interrogés. Plus récemment, une étude bicentrique conduite chez 96 patients ventilés en réanimation a retrouvé une prévalence de la dyspnée élevée (47 %). Cette dyspnée était intense puisqu'évaluée à une valeur médiane de 5 sur une échelle visuelle analogique (EVA) allant de zéro à dix (5) (voir infra, Annexe 1).

Il est important de souligner que dans toutes ces études, l'évaluation de la dyspnée sous assistance ventilatoire reposait sur l'interrogatoire des patients, excluant par conséquent les patients non communicant car insuffisamment réveillés ou confus. On peut dés lors faire l'hypothèse d'une sous évaluation de la prévalence de la dyspnée dans ces études.

Tout comme celui de la douleur, l'impact immédiat de la dyspnée en tant que « souffrance » fait peu de doute. Il suffit simplement de rappeler les propos terrifiants que rapportent certains patients exposés à une dyspnée, comme « … je ne souhaiterais pas continuer à vivre si cela devait s'éterniser » ou encore les souvenirs traumatisants associés à l'assistance ventilatoire mécanique tels qu'une sensation de « panique », « d'agonie », « d'insécurité », « de peur », « de suffoquer » ou « d'avoir peur d'être assassiné » (72, 73). A plus long terme, la dyspnée parait avoir un impact clinique négatif tant sur le séjour en réanimation lui-même que sur ses suites. Les patients en échec de sevrage de la ventilation mécanique sont plus fréquemment et plus sévèrement dyspnéiques et déprimés (67, 74). La dyspnée en réanimation pourrait donc être associée à un sevrage prolongé de la ventilation mécanique. Ainsi, dans une série de 96 patients interrogés, ceux qui présentaient une dyspnée

sans rapport avec les réglages du ventilateur étaient plus difficilement et par conséquent plus lentement extubés que les patients non dyspnéique (5) (voir infra, Annexe 1). Comme la douleur, la dyspnée parait donc avoir un impact sur la durée de sevrage et donc la durée de séjour. Les deux phénomènes, dyspnée et sevrage difficile, pourraient également n'être que deux marqueurs d'état. Des études spécifiques seront nécessaires pour déterminer la causalité du lien dyspnée-sevrage difficile, par exemple.

A moyen ou plus long terme, la dyspnée contribue, au même titre que l'anxiété, la douleur, la soif, le manque de sommeil et la gêne qu'induit la sonde d'intubation, à la genèse des expériences traumatisantes que rapportent environ 50% des patients sortis de réanimation (75, 76)

1.2.3 Autres sensations

La dysharmonie patient-ventilateur peut aussi induire d'autres sensations désagréables. A titre d'exemple, les patients présentant une dyspnée en réanimation sont plus fréquemment anxieux que les patients non dyspnéiques (71% vs. 24%) et la dyspnée est un facteur prédictif indépendamment d'anxiété chez les patients sous assistance ventilatoire (5). L'interaction entre anxiété et dyspnée est complexe ; des relations causales pouvant exister dans les deux sens. Ainsi, chez les sujets sains, l'anxiété stimule la ventilation et, de ce fait, peut induire une dyspnée (77). Les interventions à visée anxiolytiques ont alors un effet positif sur la fréquence respiratoire. Réciproquement, la dyspnée génère de l'anxiété et la soulager diminue la dyspnée (66, 72). Dans notre étude présentée en Annexe 1, le niveau d'anxiété diminuait parallèlement à l'amélioration de la dyspnée, ce en réponse à l'optimisation des réglages du ventilateur (5).

2 Moyens d'étude de la dysharmonie patient-ventilateur

Bien qu'encore peu étudiée, la dysharmonie patient-ventilateur semble donc avoir un impact délétère pour le patient. Optimiser l'harmonie patient-ventilateur devient par conséquent un objectif majeur du clinicien exerçant en réanimation. Pour ce faire, plusieurs outils sont disponibles; chacun d'entre eux offrant une analyse spécifique des différents acteurs impliqués dans une dysharmonie patient-ventilateur (voir supra : 1.1 Acteurs de la dysharmonie patient-ventilateur).

2.1 Effecteurs musculaires

La fonction des effecteurs musculaires peut être approchée de trois façons : par la mesure du profil ventilatoire, par la mesure de la pression pleurale au moyen d'un ballon-cathéter oesophagien, et enfin par le recueil de l'activité EMG du diaphragme et des muscles ventilatoire extra-diaphragmatiques.

2.1.1 Profil ventilatoire.

Le plus simple outil d'étude de l'harmonie patient-ventilateur est l'analyse du profil ventilatoire décrit par ces grandeurs (V_T, fréquence ventilatoire [FR], temps inspiratoire [Ti] et expiratoire [Te], ventilation minute, etc…). A titre d'exemple, la simple analyse de la FR, du V_T, du volume minute et des pressions inspiratoires permet d'identifier les situations les plus caricaturales de dysharmonie patient-ventilateur (polypnée, pause inspiratoire). En revanche, cette première évaluation simple peut être fréquemment prise à défaut. A titre d'exemple, de par sa nature subjective, la dyspnée peut être indépendante de la fréquence respiratoire et du profil ventilatoire (78). On peut donc être polypnéique et ne pas rapporter de dyspnée (hyperpnées des compensations d'acidose métabolique…), ou bien être très dyspnéique avec une fréquence respiratoire normale. De plus sous assistance ventilatoire

mécanique le profil ventilatoire du patient est modifié par le ventilateur, lui-même réglé par le médecin en charge du patient. Ainsi, en réanimation, aucun lien n'avait été retrouvé entre la dyspnée et le profil ventilatoire des patients sous assistance ventilatoire (5).

2.1.2 Mesure de la pression pleurale

Idéalement, de façon à évaluer au mieux l'harmonie entre le ventilateur et l'activité des muscles respiratoires du patient, il convient de disposer d'un témoin fiable de l'activité de ces muscles. Il peut s'agir d'un témoin de leur activité mécanique, comme la mesure de la pression pleurale au moyen d'un ballon-cathéter oesophagien (79). Cette mesure permet de mesurer la charge mécanique, déterminée elle même par la quantité réelle de ventilation et par les divers éléments de résistance et de compliance du système respiratoire. De récents progrès techniques ont rendu le maniement de cet outil plus accessible. L'interprétation de ces mesures peut néanmoins s'avérer difficile dans certaines situations.

2.1.3 EMG diaphragmatique.

Les techniques électrophysiologiques pourraient jouer ici un rôle majeur. Ainsi, l'étude EMG des effecteurs musculaire inspiratoire pourrait être un outil plus sensible et performant que la simple étude du profil ventilatoire. Jusqu'alors, ces techniques ont eu recours au recueil de l'activité EMG du diaphragme (80) par des électrodes de surface (81) ou œsophagiennes. Si ce premier système de recueil semble limité dans le cas du diaphragme, ce en raison du fort risque de contamination du signal EMG par l'activité électrique émanant d'autre muscles (81). Le recueil de l'activité EMG du diaphragme par électrodes œsophagiennes a récemment progressé avec le développement du mode NAVA (neuro-

asservissement de la ventilation assistée). Ce nouveau mode ventilatoire asservit le niveau d'assistance à l'intensité de l'EAdi. Il implique un enregistrement continu de l'EAdi au moyen d'un cathéter consistant en une sonde œsophagienne équipée d'électrodes, lequel EAdi est ensuite traité par un module spécifique relié au ventilateur. Ce dernier module permet au ventilateur d'adapter le niveau d'assistance à l'amplitude de l'EAdi. Le recueil continu et l'analyse de l'EAdi, indice dérivé de l'intensité de la commande ventilatoire centrale, est donc possible en VSAI comme en mode NAVA. L'EAdi peut être aisément quantifié, des manières suivantes : pic de l'EAdi ($EAdi_{max}$), aire sous la courbe du temps inspiratoire de l'EAdi ($EAdi_{AUC}$), différence entre l'EAdi maximal et l'EAdi minimal (ΔEAdi)…

2.1.4 EMG des muscles extra-diaphragmatiques.

L'analyse de l'activité EMG des muscles extra-diaphragmatiques recueillie par électrodes de surface pourrait représenter une alternative intéressante. En effet, la relation entre charge et activité de ces muscles (voir supra 1.1.2.1 Muscles inspiratoires extra-diaphragmatique) est particulièrement séduisante dans le contexte de la dysharmonie patient-ventilateur : minimiser leur activité EMG pourrait être un des objectifs du clinicien.

2.2 Equilibre charge capacité

Nous proposons ici deux modalités d'étude de l'équilibre charge capacité : l'étude du lien entre proportionnalité et couplage électromécanique et l'analyse de la variabilité cycle à cycle.

2.2.1 Proportionnalité et couplage neuromécanique.

A partir de l'EAdi, il est possible d'approcher de façon simple la notion d'équilibre charge capacité. La première approche est d'étudier la relation entre le niveau de pression inspiratoire délivrée par le ventilateur et l'EAdi. A tire d'exemple, il n'existe pas de relation entre ces deux grandeurs en VSAI car la pression d'assistance reste constante, ce quelle que soit la pression musculaire développée par le patient. En revanche, le développement récent de modes dit « proportionnels », dans lesquels l'assistance délivrée par le ventilateur augmente à mesure que la demande ventilatoire du patient augmente, et réciproquement, permet d'améliorer cet aspect de la synchronisation patient-ventilateur. La seconde approche consiste quant à elle en l'évaluation de la qualité du couplage neuro-mécanique par le calcul d'indices dérivés de l'EAdi en les rapportant au volume courant.

2.2.2 Etude de la variabilité ventilatoire cycle à cycle

Au repos, la ventilation spontanée n'est pas monotone. Il est ainsi rare d'observer deux cycles respiratoires successifs en tout point superposables et identiques. Les grandeurs utilisées pour décrire le profil ventilatoire varient dans le temps, spontanément ou à l'occasion de changements environnementaux. Cette variabilité, dite « cycle à cycle », décrite dès la fin du XIXème siècle (82), est éminemment physiologique (83, 84) et peut être très simplement appréhendée par le calcul du coefficient de variation qui se définit comme l'écart-type rapporté à la moyenne (85) (Table 1). Les valeurs « normales » du coefficient de variation des principaux descripteurs du profil ventilatoire ne sont pas formellement établies. Néanmoins, les valeurs rapportées par Tobin et al. chez 65 volontaires sains, après 15 minutes de ventilation spontanée, peuvent servir de référence (84, 86). Le coefficient de variation du V_T, de la FR et du Ti rapporté à la durée totale du cycle (Ti/Ttot) étaient respectivement de 33,0 ± 14,9 %, 20,8 ± 11,5 %, et 17,7 ± 6,5 %. Cette même variabilité peut aussi être décrite par la force de la relation qui existe entre un cycle ventilatoire et le suivant,

autrement appelée autocorrélation (concept de « mémoire à court terme ») (85). Ainsi, l'autocorrélation peut être décrite par le « r-lag^{-1} » qui correspond au coefficient d'autocorrélation entre un cycle et le suivant ou encore par le « lag » défini par le nombre de cycles respiratoires séparant deux cycles significativement corrélés. Plus complexe, l'analyse spectrale par transformée de Fourier permet de décomposer le profil ventilatoire selon ses pics de fréquence en trois fractions : périodique, auto corrélée et aléatoire (87). Cette approche, qui a fait très largement ses preuves dans le domaine de la variabilité cardiaque, semble en pratique efficace pour décrire la variabilité ventilatoire. Cette variabilité ventilatoire est physiologique et semble témoigner d'un faible niveau de contrainte imposé à l'appareil respiratoire (83, 84). En revanche, la diminution de cette même variabilité est pathologique et témoigne d'une augmentation du niveau de charges imposée à l'appareil respiratoire (88-90). Dans ce sens, les contraintes ventilatoires, quelle que soit leur nature, tendent à diminuer la variabilité du comportement ventilatoire. C'est ainsi que l'hypercapnie diminue la variabilité ventilatoire alors que l'hypocapnie l'augmente (91, 92). De la même façon, on observe une diminution de la variabilité ventilatoire lors de l'application, chez des sujets sains, de charges mécaniques résistives (89) ou élastiques (88). Ainsi, l'étude de la variabilité ventilatoire offre une approche de l'équilibre charge-capacité. A titre d'exemple, le sevrage de la ventilation mécanique est une situation caractéristique où le système respiratoire doit faire face à une somme de charges mécaniques ou métaboliques. Le succès de cette épreuve est principalement déterminé par la nature du rapport entre les charges imposées au système respiratoire et la capacité des muscles ventilatoires à les surmonter. L'utilisation des indices de variabilité dans le but de prédire le succès du sevrage de la ventilation mécanique a été largement étudiée. Il est ainsi montré que les malades extubés avec succès ont une variabilité ventilatoire supérieure à celle des patients en échec d'extubation (93-95). Un coefficient de variation du rapport V_T /Ti $\geq$ 19% et du rapport

Ti/Ttot ≥ 10% après une épreuve de ventilation spontanée sur pièce en T de 60 minutes prédit assez précisément le succès du sevrage (95).

2.3 Commande centrale

2.3.1 Analyse de la complexité de la commande ventilatoire.

La variabilité cycle-à-cycle du comportement ventilatoire provient du fait que la commande ventilatoire centrale n'est pas produite par des oscillateurs "sinusoïdaux", mais par des oscillateurs dits "complexes" qui produisent un signal de sortie "anharmonique". On utilise le terme "système complexe" pour désigner des ensembles constitués d'un grand nombre d'entités en interaction, dont le comportement ou l'évolution est imprévisible, tout en restant inscrit dans une gamme prédictible. Ainsi, si l'on représente l'évolution d'un signal physiologique cyclique et "complexe" au cours du temps dans un espace tridimensionnel, on constate que chaque "cycle" est représenté par une figure irrégulière qui ne recouvre pas la précédente et n'est pas recouverte par la suivante. Au contraire, le "portrait de phase à trois dimensions" d'un signal cyclique "linéaire", ou "périodique" est simple et "monotone". On peut décrire la complexité d'un signal au moyen d'outils mathématiques non linéaires pour la plupart dérivés de la théorie du chaos. Très schématiquement, on parle de "chaos" pour décrire une dynamique périodique anharmonique dans un système déterministe sensible aux conditions initiales (96). Des débats animés opposent physiciens et mathématiciens sur la définition du chaos et la façon de le mettre en évidence. Pour certains, qualifier de "chaotique" la ventilation des mammifères est impropre, parce qu'il n'est pas possible de prouver mathématiquement un "déterminisme" (un "but", une "orientation" en langage simple) qui est pourtant physiologiquement évident ("assurer la vie et l'homéostasie"). Il faudrait en toute rigueur employer des termes comme "pseudo-chaotique", ou "chaos compatible" ; en pratique, parler de complexité suffit à exprimer le message souhaité. De

nombreuses données scientifiques démontrent le caractère complexe de la ventilation [18-19]. Chez l'humain, le sommeil lent profond, qui supprime les influences afférentes et corticales qui s'exercent sur le contrôle ventilatoire, est associé à une diminution marquée de la complexité ventilatoire (97), ce qui est aussi le cas de l'hypocapnie (91).

L'automatisation des calculs et le développement de nouvelles méthodes d'analyse ont rendu plus accessible l'étude non linéaire de la variabilité ventilatoire. Une méthode récente, dite « titration de bruit » (en anglais « noise titration» donnant accès à la "noise limit") (98) donne accès à une évaluation quantitative de la complexité ventilatoire, et permet, si certaines précautions méthodologiques sont respectées, de caractériser d'éventuels changements d'état. Brièvement, cette technique recherche la présence d'une composante non linéaire de la variabilité puis mesure la quantité de « bruit blanc » nécessaire à la masquer. Un peu comme la titration d'un acide par une base. Une « noise limit » supérieure à zéro témoigne du caractère non linéaire du signal traité (par exemple le débit ventilatoire) et sa valeur est proportionnelle au degré de complexité. Une fois affirmée la complexité du signal, on peut en décrire d'autres caractéristiques, comme par exemple la sensibilité aux conditions initiales. En d'autres termes, il s'agit d'évaluer à quel point une perturbation dans le passé peut affecter le comportement futur d'un système. La sensibilité aux conditions initiales peut être décrite par le calcul du plus grand des exposants de Lyapunov (LLE) (99). Plus le LLE est élevé, plus le système est sensible aux conditions initiales. Une autre caractéristique d'un système complexe est son imprédictibilité. Celle-ci est estimée par la somme des exposants de Lyapunov positifs, autrement appelée entropie de Kolmogorov-Sinai (KSE) (100). Ainsi une faible KSE témoigne d'un système prédictif et régulier, à l'inverse un KSE élevé reflète un système imprédictible et fortement variable. Enfin, cette complexité peut être représentée par le portrait de phase en trois dimensions, représentation graphique de la nature du système.

Chez les patients de réanimation, l'échec du sevrage de la ventilation mécanique semble être associé à une complexité supérieure du V_T (101). Par ailleurs, alors que les patients ventilés de façon contrôlée ne présentent majoritairement pas de complexité ventilatoire, le passage en VSAI s'accompagne chez les mêmes patients de l'apparition d'une telle complexité (102). Ceci suggère donc que, même chez les patients mécaniquement ventilés en réanimation, la complexité ventilatoire est fortement liée à l'activité des centres de la commande ventilatoire, isolés ou sous l'influence des afférences d'origine respiratoire (91). Ceci implique de souligner l'importance de la nature du signal étudié pour interpréter la complexité ventilatoire et son évolution au cours du temps. Ainsi, plus le signal étudié est "en aval" de la commande ventilatoire, moins l'information fournie porte-t-elle "purement" sur celle-ci. La complexité du débit ventilatoire semble être plus descriptive du couplage neuromécanique (équilibre charge-capacité) que de la commande centrale. En revanche, l'étude de la complexité de l'EAdi pourrait refléter la commande centrale.

3 Des modes de ventilation partielle aux modes de ventilation proportionnelle

Les modes ventilatoires partiels regroupent l'ensemble des modes ventilatoires autorisant une participation du patient à l'effort ventilatoire, que ce soit pour le déclenchement du ventilateur ou sa contribution à la genèse du volume courant. Ainsi, en ventilation partielle, la pression musculaire développée par le patient n'est pas nulle, contrairement aux modes contrôlés où seul le ventilateur produit le volume courant. Selon les rapports existants entre la pression d'assistance délivrée par le ventilateur (P_{vent}) et la pression musculaire fournie par le patient (P_{mus}), deux groupes d'assistance partielle peuvent être distingués :

- Le premier est représenté par la VSAI. Ici, la pression d'assistance reste constante quelle que soit la pression musculaire développée par le patient. Quand le patient augmente

son effort musculaire, le V_T augmente, mais avec un rendement qui reste constant, identique à celui du patient sans assistance.

- Le second regroupe les modes reposant sur la proportionnalité de l'assistance à l'effort inspiratoire du patient. Dans ces modes dits « proportionnels », l'assistance délivrée par le ventilateur augmente à mesure que la demande ventilatoire du patient augmente, et réciproquement. De ce fait, la pression d'assistance délivrée par le ventilateur devient variable, adaptée aux variations de demande ventilatoire survenant au cours du temps, à la fois entre chaque cycle et au sein même d'un cycle respiratoire. Les modes de ventilation proportionnelle sont au nombre de deux : la ventilation assistée proportionnelle (PAV) (103, 104) (Puritain Bennett 840, Covidien, Colorado, USA) et la NAVA (105) (Servo-i, Maquet Critical Care, Solna, Suède).

En agissant au plus proche de la commande ventilatoire du malade, ces modes proportionnels s'affranchissent d'un des principaux écueils des modes dits « conventionnels » – e.g. la VSAI – qui est d'admettre à tort que la demande ventilatoire reste stable au cours du temps et par conséquent de délivrer une assistance fixe. Pour ce faire, la PAV et le NAVA fonctionnent comme des amplificateurs de la commande ventilatoire en délivrant une pression proportionnelle à l'activité musculaire inspiratoire en PAV ou à l'EAdi en NAVA.

Le développement de ces modes proportionnels a mis au premier plan la notion d'harmonie patient-ventilateur.

3.1 La ventilation assistée proportionnelle (PAV)

3.1.1 Principes généraux

La PAV est un mode de ventilation partielle dans lequel le ventilateur délivre un niveau d'assistance proportionnel à l'effort musculaire instantané du patient. Cette

proportionnalité s'applique de façon continue au cours de l'inspiration (103, 104) et nécessite de connaître l'effort fourni par le patient ainsi que la mécanique de son système respiratoire.

Son principe est en grande partie fondé sur l'équation du mouvement du système respiratoire (voir encart : Equation 1).

La mesure des débits et des volumes instantanés produits par le patient permet d'estimer son effort musculaire (voir encart : Equation 2). Ceci nécessite la mesure de l'élastance et de la résistance de l'appareil respiratoire, laquelle est réalisée de façon automatique, non-invasive et semi-continue au moyen de micro-occlusions télé-inspiratoires de 300 ms, tous les 4 à 10 cycles, de manière aléatoire (106, 107).

Equation (1) : Equation du mouvement du système respiratoire

$$\mathbf{P_{tot} = P_{vent} + P_{mus} = P_{vent} - |P_{mus}| = (E \times V) + (R \times V') + P_0}$$

La pression totale appliquée au système respiratoire (P_{tot}) – correspondant à la somme de la pression produite par les muscles respiratoires (P_{mus}) et délivrée par le ventilateur (P_{vent}) – nécessaire à la mobilisation d'un certain volume (V) et d'un certain débit (V') dans le système respiratoire – présentant lui-même à l'inspiration une certaine élastance (E) et résistance (R) – est la somme de la pression de départ (P_0), de la pression nécessaire pour produire ce débit, c'est à dire pour vaincre les forces résistives (R x V') et de la pression nécessaire pour produire le volume c'est à dire pour contre balancer les forces de rétraction élastique (E x V).

Equation (2) : Estimation de la pression musculaire fournie par le patient

$$\mathbf{Pmus = V_{patient} \times E + V'_{patient} \times R}$$

$V_{patient}$: volume généré par le patient, $V'_{patient}$: débit généré par le patient

Equation (3) : Détermination de la pression délivrée par le ventilateur en PAV

$$\mathbf{Pvent = gain \times Ptot + P0}$$

Pvent = (gain / (1 – gain) x |Pmus| + P0
Où gain / (1 – gain) correspond à la constante de proportionnalité *k*

3.1.2 Déclenchement du ventilateur

En PAV, le principe de déclenchement du ventilateur est le même que celui utilisé en VSAI et repose sur des signaux classiques de débit aux voies aériennes.

3.1.3 Mise en pression des voies aériennes

Le ventilateur délivre une assistance proportionnelle à l'effort musculaire instantané du patient, et ce de façon continue tout au long du cycle respiratoire selon une constante de proportionnalité *k* (103, 104). En pratique, le réglage du ventilateur ne s'effectue pas sur cette constante de proportionnalité mais plutôt sur un gain représentant la proportion de la pression totale appliquée prise en charge par le ventilateur (voir encart : Equation 3). Ainsi, pour un réglage du ventilateur donné, la PAV s'adaptera automatiquement aux variations de charge ou de demande ventilatoire (108-111).

3.1.4 Cyclage (ou transition de l'insufflation vers l'expiration)

En mode PAV, le cyclage reste pneumatique – *i.e.* basé sur les signaux de débit et de pression aux voies aériennes –, mais sa singularité réside dans les propriétés de cyclage expiratoire : l'ouverture de la valve expiratoire, donc la fin de l'insufflation et la transition vers l'expiration, est déterminée par la fin du débit inspiratoire. En d'autres termes, le cycle s'arrête en PAV dès que l'effort du patient se termine, ce qui n'est pas le cas en VSAI où l'insufflation peut se poursuivre au-delà du temps inspiratoire du patient, facteur majeur d'hyperinflation dynamique (112).

3.2 Le neuro-asservissement de la ventilation assistée (NAVA)

3.2.1 Principes généraux

Dans le contexte d'une approche scientifique de la dysharmonie patient-ventilateur, le NAVA offre un modèle unique d'harmonie patient-ventilateur. En effet, décrit en 1999 (105), le mode NAVA délivre une assistance ventilatoire proportionnelle à l'EAdi. Ce mode ventilatoire a été commercialisé en 2006 au terme de nombreux travaux expérimentaux, et les premiers travaux cliniques en réanimation adulte ont été publiés en 2008 (113). Le mode NAVA est disponible sur les ventilateurs Servo-i (Maquet Critical Care, Solna, Suède). En plus d'être un moyen de mesure de l'activité du diaphragme l'EAdi est un témoin direct de l'intensité de la commande ventilatoire centrale (114). Ainsi, il est classiquement admis que ce mode asservit l'assistance à un signal plus « proche » de la commande que ne sont les variations de débit et de pression aux voies aériennes.

Le mode NAVA nécessite en premier lieu le recueil de l'EAdi. Ce recueil est réalisé au moyen d'une sonde gastrique d'alimentation équipée de huit paires d'électrodes EMG. Ce dispositif médical porte le nom de « cathéter EAdi ». Une fois la sonde en place, ces électrodes, situées en regard du diaphragme recueillent l'activité EMG de ce muscle. Les signaux provenant de chaque paire d'électrodes sont amplifiés et secondairement transmis à un module, second composant de la NAVA. Ce module, lui-même connecté au ventilateur, en permet le pilotage. L'utilisation de filtres ainsi que d'un algorithme de double soustraction de ce signal brut permettent de supprimer les divers artéfacts et d'obtenir le meilleur rapport signal-bruit possible (115, 116). Le signal d'EAdi ainsi recueilli est secondairement appliqué au ventilateur, permettant le contrôle des trois principales phases de l'assistance ventilatoire : le déclenchement, la mise en pression des voies aériennes et le cyclage (117).

3.2.2 Déclenchement du ventilateur

En mode NAVA, l'ouverture de la valve inspiratoire et la pressurisation des voies aériennes est déclenchée lorsque survient une variation d'EAdi au delà d'un seuil au-dessus de la valeur de base d'EAdi. Le déclenchement du ventilateur est donc déterminé par un signal plus proche de la commande ventilatoire centrale que ne sont les variations de débit et de pression aux voies aériennes résultant de l'expansion thoracique secondaire à la contraction du diaphragme.

3.2.3 Mise en pression des voies aériennes

Une fois la valve inspiratoire ouverte, le niveau d'assistance ventilatoire fourni est proportionnel à l'intensité de l'EAdi. Cette constante de proportionnalité est un paramètre réglable (de 0 à 30 $cmH_2O/\mu V$) et correspond à ce que l'on appelle le niveau de NAVA (ou gain). Cette boucle de régulation s'effectue au sein même de chaque cycle et entre les différents cycles, s'adaptant ainsi en temps réel à la commande centrale du patient. Ceci s'oppose aux niveaux d'assistance constants délivrés par les modes ventilatoires classiques tels que la VSAI et dont le principal inconvénient est de ne pas s'adapter en temps réel à la demande du patient.

3.2.4 Cyclage (ou transition de l'insufflation vers l'expiration)

Il repose sur un seuil fixe (non modifiable) de 70 % du pic d'EAdi (ou 40% si le pic d'EAdi est trop faible < 1,5 µV). Lorsque l'EAdi diminue en deçà de ce seuil, le ventilateur interrompt la pressurisation des voies aériennes et autorise l'expiration.

3.3 Mode de ventilation proportionnelle et harmonie patient-ventilateur

3.3.1 Ventilation assistée proportionnelle et harmonie patient-ventilateur

Lors de la PAV, le ventilateur délivre une assistance en pression proportionnelle à l'effort musculaire instantané du patient. Cette proportionnalité s'applique de façon continue au cours de l'inspiration (103, 104) et nécessite de connaître l'effort fourni par le patient ainsi que la mécanique de son système respiratoire (compliance et résistance).

3.3.1.1 Bénéfices du mode PAV

Plusieurs études se sont intéressées à l'impact physiologique de la PAV et à la contribution de ce mode à une meilleure harmonie patient-ventilateur. Ces études ont retrouvé les effets suivants.

- Prévention de la surdistention thoracique : la PAV est asservie à l'effort inspiratoire du patient. Ainsi, une augmentation du niveau d'assistance entraînera une diminution de l'effort inspiratoire, une augmentation modérée de la pression d'assistance sans effet ou presque sur le volume courant (118).

- Amélioration de l'interaction patient-ventilateur : en limitant le risque de distension dynamique, la PAV permet de prévenir la survenue d'asynchronies patient-ventilateur (118-121) et pourrait ainsi améliorer la qualité du sommeil des patients en réanimation (122).

- Restauration de la variabilité naturelle de la ventilation : Chez 13 patients mécaniquement ventilés successivement en PAV et en VSAI dans des conditions d'assistance comparables (pression inspiratoire moyenne similaire dans les deux conditions), le V_T moyen était identique dans les deux conditions tandis que sa variabilité était significativement supérieure en PAV (10 ± 4% vs 20 ± 13%) (123). De plus, la baisse du niveau d'assistance en PAV (diminution de la proportion de « l'effort inspiratoire » prise en charge par le ventilateur), affectait peu la variabilité du V_T qui restait supérieure en PAV par rapport au mode VSAI (123). Ainsi, en s'adaptant à l'activité musculaire respiratoire propre du patient sans lui imposer une assistance fixe comme le fait la VSAI, le mode PAV permet de restaurer

la variabilité du comportement ventilatoire [26-30]. Plusieurs études comparant les modes PAV et VSAI en ventilation non invasive dans une population générale de patients de réanimation (124, 125) ou spécifiquement chez des patients ayant une broncho-pneumopathie chronique obstructive (126, 127) ont démontré, en se basant sur une échelle visuelle analogique, une amélioration du confort respiratoire en PAV. Un meilleur respect de la variabilité ventilatoire en PAV pourrait en être à l'origine.

Enfin, en termes de bénéfices cliniques, une étude a montré que, comparé à la VSAI, le mode PAV permettait de maintenir les patients en ventilation spontanée avec plus de succès et réduisait ainsi les retours en mode contrôlé (121). En revanche, aucun essai n'a montré une supériorité de la PAV sur la VSAI sur des critères tels que la mortalité ou le taux d'intubation (124, 125). Il est toutefois important de souligner que l'utilisation de la PAV s'accompagne d'une diminution des interventions thérapeutiques telles que les changement de réglage du ventilateur et les ajustements de posologie des médicaments sédatifs (128). Il pourrait donc exister un bénéfice de la PAV sur la charge en soins.

3.3.1.2 Limites du mode PAV

Une des limites de ce mode est liée aux signaux servant à l'asservissement du ventilateur pour contrôler l'assistance. En effet, les signaux de débit, pression et volume nécessitent la transformation de l'activation neuro-musculaire en mouvement. Ils sont donc tardifs par rapport à l'activation neuro-musculaire et vont dépendre du couplage neuro-mécanique du diaphragme et de la mécanique du système respiratoire. Une atteinte du couplage neuro-mécanique du système respiratoire risque d'altérer la réponse du ventilateur : avec une même commande ventilatoire, le signal de contrôle et donc la pression d'assistance seront diminués en PAV (110, 129). Il semble que les améliorations apportées par le mode PAV+ permettent de préserver ce couplage neuro-mécanique (111).

En théorie, le mode PAV ne permet pas de s'affranchir des phénomènes de pression expiratoire positive intrinsèque (PEPi). Cette PEPi constitue une charge à seuil que le patient doit surmonter avant de pouvoir générer une pression négative et un débit inspiratoire, et sera alors source d'efforts inefficaces. Le fait que le mode PAV prévienne la surdistension, génératrice de PEPi, en limite largement les conséquences.

3.3.2 Neuro-asservissement de la ventilation assistée et harmonie patient-ventilateur

Alors que la PAV a été développé dans les années 90, les premières études sur le NAVA chez les patients adultes ne sont apparues que quinze ans plus tard. Contrairement à la PAV qui délivre une assistance proportionnelle à l'effort musculaire inspiratoire, le NAVA délivre une assistance ventilatoire proportionnelle à EAdi, témoin direct de l'activité de la commande ventilatoire centrale (114). Ce rapprochement de la commande centrale devrait se traduire théoriquement pas une ventilation plus « naturelle » et donc une optimisation de l'harmonie patient-ventilateur. Traduire ce concept « théorique » en preuve scientifique à été un des objectifs de nos travaux. Dans le même temps, d'autres équipes travaillant également sur le NAVA ont permis d'identifier, comme en PAV, les bénéfices et limites potentiels de ce mode.

3.3.2.1 Bénéfices du mode NAVA

Les études réalisées à ce jour sont principalement de nature physiologique. Elles ont montré les bénéfices suivants.

- Amélioration qualitative et quantitative de l'interaction patient-ventilateur : du fait de son asservissement à un signal proche de la commande ventilatoire centrale, le mode NAVA améliore les délais entre le début ou la fin de l'inspiration, le déclenchement ou le

cyclage du ventilateur et réduit la prévalence des asynchronies patient-ventilateur (113, 130-132).

- Prévention du risque de sur-assistance : contrairement à la VSAI, on constate en mode NAVA que l'augmentation du niveau d'assistance ne s'accompagne pas systématiquement d'une augmentation du volume courant (113, 131, 132). Les mécanismes de cet effet protecteur de la NAVA ne sont pas univoques.

- Amélioration des échanges gazeux : en postopératoire, l'utilisation du mode NAVA s'accompagne d'une amélioration des échanges gazeux, qu'il s'agisse de l'oxygénation ou des niveaux de $PaCO_2$ (133).

- Restauration de la variabilité naturelle de la ventilation : contrairement à la VSAI, le mode NAVA restaure presque en totalité la variabilité naturelle de la ventilation (133, 134). Cet aspect de l'harmonie patient-ventilateur constitue le premier travail de cette thèse (voir infra, chapitre I).

3.3.2.2 Limites du mode NAVA

Le bon fonctionnement du mode NAVA reste entièrement dépendant du signal EAdi. Son recueil nécessite l'ajout d'un dispositif – *i.e.* cathéter EAdi – et reste donc par définition invasif.

Alors que l'obtention de ce signal s'avère rarement difficile en dehors de certaines situations – *e.g.* en cas de hernie diaphragmatique –, c'est la stabilité du signal EAdi au cours du temps, ainsi que l'intégrité des électrodes œsophagiennes qui peuvent poser problème en pratique clinique, pour des malades nécessitant une ventilation prolongée.

Le mode NAVA est asservi sur l'activité d'un seul muscle inspiratoire, le diaphragme. Bien qu'étant le principal muscle inspiratoire chez l'homme, il n'est pas le seul et

l'inspiration normale nécessite l'action coordonnée du diaphragme et de muscles inspiratoires extra-diaphragmatiques, et ce d'autant plus que des charges sont imposées à l'appareil respiratoire. Il est possible que l'EAdi, sur laquelle est asservi le mode NAVA, ne soit le reflet seulement d'une partie de l'effort inspiratoire du patient, notamment en cas d'insuffisance respiratoire aigue.

Enfin, le bénéfice clinique de l'utilisation du NAVA sur des critères robustes tels que la mortalité ou la durée de ventilation mécanique n'a pas été démontré à ce jour.

4 Identification et quantification d'une dyspnée sous assistance ventilatoire

Toutes les données précédemment exposées plaident pour une diminution de la dysharmonie patient-ventilateur et donc une surveillance régulière de la dyspnée en réanimation. Néanmoins, la surveillance de la dyspnée en réanimation n'est pas aisée. En effet, outre les difficultés associées à l'évaluation d'un symptôme —subjectif par nature—, les multiples stimulus auxquels sont exposés les patients de réanimation placés sous assistance ventilatoire mécanique (modification de la sédation, de l'analgésie, mobilisation, effort, complications intercurrentes…) implique que la sensation dyspnéique est par nature labile et susceptible de connaître de nombreuses variations sur des intervalles de temps brefs.

4.1 L'échelle visuelle analogique de dyspnée

A ce jour, la méthode la plus fiable pour détecter une dyspnée sous assistance ventilatoire mécanique est finalement… d'interroger le patient ... quand c'est possible (5). En effet, les pré-requis nécessaires sont un bon niveau de vigilance et une absence de confusion.

Une fois la dyspnée détectée, sa quantification peut être réalisée au moyen d'un échelle visuelle analogique (EVA), graduée de 0 (« pas d'effort pour respirer », « pas de

dyspnée », « pas de gêne respiratoire ») à 10 (« effort très intense» ou « dyspnée la pire que vous puissiez imaginer", ou "gêne respiratoire intolérable") ou l'échelle de Borg (échelle semi quantitative proche de l'EVA mais avec 10 propositions allant en ordre croissant de sévérité, de « pas de gêne du tout » à « extrêmement gêné »). Ces deux échelles sont simples d'utilisation et reproductibles. Leur simplicité de compréhension pour le patient et les soignants (généralement familiers de cette approche pour la douleur) leur confère un grand intérêt (5, 135). L'EVA, est bien corrélée avec les autres échelles de dyspnée (69, 70). Pour mieux caractériser la dyspnée, des questionnaires plus « évolués » ont été développés, tels que le MDP (Multidimensional Dyspnea Profile) ou l'échelle dite "RDOS" (Respiratory Distress Observation Scale). Néanmoins, ces échelles, n'ont pas encore été validées chez le patient ventilé.

4.2 L'examen clinique : un intérêt limité

Malheureusement, de par sa nature subjective, la dyspnée peut être indépendante de la fréquence respiratoire et du profil ventilatoire (78). De plus sous assistance ventilatoire mécanique le profil ventilatoire du patient est modifié par le ventilateur, lui-même réglé par le médecin en charge du patient. Ainsi, en réanimation, aucun lien n'avait été retrouvé entre la dyspnée et le profil ventilatoire des patients sous assistance ventilatoire (5). Sous réserve d'une éventuelle validation en réanimation de l'échelle RDOS ou d'outils analogue, l'examen clinique apparaît peu pertinent en tant qu'outil de dépistage de la dyspnée (5). Cet obstacle ne doit néanmoins pas arrêter le clinicien. En effet, comme dans le cas de la douleur, ne pas pouvoir dire que l'on a du mal à respirer n'empêche pas d'en souffrir. Il ne semble donc pas illicite de chercher une anomalie potentiellement source de dyspnée et de chercher à la corriger, chez un patient présentant des signes de détresse respiratoire et/ou une expression de souffrance.

4.3 Les outils neurophysiologiques : des perspectives intéressantes

Face à la difficulté de détecter et quantifier la dyspnée chez les patients non communicants, certaines équipes ont orienté leurs recherches vers des outils de mesures objectifs utilisables au lit du patient de réanimation. La plupart de ces outils reposent sur des corrélats neurophysiologiques de la dyspnée et sont, dans le meilleur des cas, au stade de développement.

L'activité EMG des muscles inspiratoires extradiaphragmatiques est intéressante en ce qu'il existe une forte corrélation entre l'activation de ces muscles et la présence et l'intensité d'une dyspnée (13, 14, 136-139). Le monitorage d'index EMG pourrait ainsi servir de signal d'alarme, une augmentation de l'activité de muscles comme les scalènes, les parasternaux intercostaux, ou *Alae nasi* —tous facilement accessible à l'enregistrement— incitant le clinicien à rechercher une cause à cette dyspnée. La validation de l'EMG des muscles extradiaphragmatiques comme outils de détection de la dyspnée en ventilation mécanique fait l'objet d'un travail spécifique de cette thèse (voir infra, chapitre 4).

Position du problème

L'étude de la dysharmonie patient-ventilateur et de ses déterminants chez les patients de réanimation a progressé au cours de ces 15 dernières années. Initialement limitée au cadre d'une recherche fondamentale ou théorique, la dysharmonie patient-ventilateur semble désormais devenir une préoccupation du clinicien.

Il est en effet paradoxal qu'une assistance ventilatoire mécanique, initiée pour suppléer tout ou partie de la fonction respiratoire lorsque l'appareil respiratoire est défaillant, puisse être en elle-même une cause de dyspnée et d'inconfort. Ce paradoxe a conduit au développement de nouveaux modes ventilatoire dit « proportionnels » et à l'étude d'une conséquence jusqu'ici méconnue de la dysharmonie patient-ventilateur : la dyspnée.

La recherche dans ce domaine est récente et de nombreuses questions restent à ce jour sans réponse claire. Au travers des travaux qui constituent le corps de cette thèse nous nous sommes posés deux questions : 1) En se rapprochant de la commande centrale et en générant une ventilation dite plus « naturelle », les modes de ventilation proportionnelle, seraient-ils un modèle d'harmonie patient-ventilateur ? ; 2) La dyspnée, principale sensation respiratoire associée à une dysharmonie patient-ventilateur peut être difficile à évaluer en ventilation mécanique. Y a t il des indices permettant de mieux la détecter en ventilation mécanique ?

Hypothèses

Les données que nous venons d'exposer suggèrent qu'une inadéquation entre l'activité des muscles respiratoires, l'intensité de la commande centrale et l'assistance délivrée par le ventilateur se traduit par la survenue d'une dysharmonie patient-ventilateur. Une telle dysharmonie est fréquente en réanimation. L'engouement récent pour les modes de ventilation proportionnelle pourrait contribuer à réduire sa survenue. De même, une détection précoce de la dyspnée en ventilation mécanique, principale conséquence de cette dysharmonie, pourrait également contribuer à l'amélioration du confort des patients.

Nous avons par conséquent formulé les hypothèses suivantes :

1. en comparaison avec la ventilation assistée en aide inspiratoire et à travers l'étude de la variabilité du comportement ventilatoire et des asynchronies patient-ventilateur, le NAVA améliore l'interaction patient-ventilateur en ventilation invasive ;
2. ce bénéfice du NAVA est également observé en VNI ;
3. le NAVA et la PAV ont des effets similaires sur l'interaction patient-ventilateur ;
4. l'augmentation de l'activité EMG des muscles inspiratoires extra-diaphragmatiques est corrélée au niveau de dyspnée, faisant de cette activité un outil potentiel de détection de la dysharmonie patient-ventilateur et des sensations respiratoires correspondantes.

De façon à vérifier ces hypothèses, nous avons conduit quatre études sur des patients ventilés en réanimation pour une insuffisance respiratoire aigue. Nous avons fait le choix d'étudier l'intérêt des modes proportionnels dans deux modalités d'administration de la

ventilation mécanique : la ventilation invasive sur sonde endo-tracheale et la ventilation non invasive au masque.

Chapitre 1

Le NAVA améliore l'équilibre charge-capacité et le couplage neuromécanique. Ce mode révèle et autorise « l'expression » de la variabilité naturelle et de la complexité de la commande centrale du patient.

La ventilation n'est pas monotone mais variable au cours du temps. Cette variabilité est inhérente à la nature de la commande centrale et associe une variabilité cycle à cycle à une complexité habituellement dénommée « chaos ». Le NAVA asservit l'assistance ventilatoire à l'activité éléctromyographique du diaphragme (EAdi), témoin direct de l'activité de la commande ventilatoire centrale. Il est donc licite de faire l'hypothèse que le NAVA devrait permettre d'obtenir une ventilation plus « naturelle » ou variable que les autres modes. L'objectif de l'étude était de quantifier la variabilité ventilatoire lors d'une ventilation par plusieurs niveaux de NAVA chez des patients préalablement ventilés en aide inspiratoire (VSAI) au décours d'un épisode d'insuffisance respiratoire aiguë.

Chez 12 patients intubés, le débit ventilatoire et l'EAdi ont été recueillis en VSAI puis à 4 niveaux de NAVA croissants (NAVA 1, 2, 3, 4 cmH2O/µV d'Edi). Nous avons ensuite étudié : 1) les principaux descripteurs du profil ventilatoire : V_T, FR et période (Ttot) respiratoire, du temps inspiratoire (Ti), de Vt/Ti et de Ti/Ttot ; 2) la variabilité cycle à cycle, quantifiée au moyen du coefficient de variation et d'une analyse d'autocorrélation de l'EAdi ainsi que des principaux descripteurs du profil ventilatoire et; 3) la complexité, recherché par la titration de bruit puis la sensibilité aux conditions initiales quantifiée par le calcul du plus grand exposant de Lyapunov.

Comparé à la VSAI, le NAVA modifiait peu les valeurs moyennes des différents descripteurs du profil ventilatoire. Parallèlement, l'EAdi diminuait significativement lors du

passage en NAVA et à mesure que le niveau de NAVA augmentait. Le coefficient de variation des descripteurs du cycle ventilatoire était supérieur en mode NAVA comparé à la VSAI et augmentait parallèlement au niveau de NAVA. L'analyse d'autocorrélation allait dans le même sens. Chez tous les patients en VSAI et à tous les niveaux de NAVA, la « noise limit » du débit et du signal EAdi était positive, témoignant d'un système non linéaire chaotique. Le calcul du plus grand des exposants de Lyapunov du débit ventilatoire était significativement plus élevé en $NAVA_2$, $NAVA_3$, et $NAVA_4$ qu'en VSAI. A l'inverse, le passage de VSAI à NAVA et l'augmentation du gain de NAVA n'avaient pas d'impact sur la complexité du signal d'EAdi. Les portraits de phase en trois dimensions illustraient la différence entre la complexité du débit et de l'EAdi ainsi que l'impact du niveau de NAVA sur celle-ci. En VSAI, le nombre de trajectoires du débit apparaissait limité. Cela se traduisait sur les portraits de phase par une figure géométrique relativement simple. Celle ci se complexifiait en NAVA avec un nombre et une complexité des trajectoires du débit qui augmentaient avec le niveau de NAVA. Ce phénomène était beaucoup moins visible avec le signal d'EAdi. En effet, en VSAI, le portrait de phase du signal d'EAdi avait déjà en VSAI une trajectoire « complexe », laquelle était de ce fait peu modifiée par le niveau de NAVA.

Cette étude démontre donc qu'en ventilation invasive, le NAVA est associé à une variabilité et une complexité ventilatoire plus élevée que la VSAI, ce alors même que la complexité de l'EAdi, reflet direct de la commande centrale, reste constante.

On conclut donc de ce travail que le NAVA : 1) améliore l'adéquation charge-capacité et/ou le couplage neuromécanique et ; 2) révèle et permet « l'expression » de la complexité de la commande centrale du patient.

Les données issues de ce premier travail ont fait l'objet d'une publication scientifique dans *Anesthesiology (140).*

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Neurally Adjusted Ventilatory Assist Increases Respiratory Variability and Complexity in Acute Respiratory Failure

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ABSTRACT

Background: Neurally adjusted ventilatory assist (NAVA) is a partial ventilatory support mode where positive pressure is provided in relation to diaphragmatic electrical activity (EAdi). Central inspiratory activity is normally not monotonous, but it demonstrates short-term variability and complexity. The authors reasoned that NAVA should produce a more "natural" or variable breathing pattern than other modes. This study compared respiratory variability and complexity during pressure support ventilation (PSV) and NAVA.

Methods: Flow and EAdi were recorded during routine PSV (tidal volume ~6–8 ml/kg) and four NAVA levels (1–4 cm H_2O/μVEAdi) in 12 intubated patients. Breath-by-breath variability of flow and EAdi-related variables was quantified by the coefficient of variation (CV) and autocorrelation analysis. Complexity of flow and EAdi was described using noise titration, largest Lyapunov exponent, Kolmogorov-Sinai entropy, and three-dimensional phase portraits.

Results: Switching from PSV to NAVA increased the CV and decreased the autocorrelation for most flow-related variables in a dose-dependent manner ($P < 0.05$, partial η^2 for the CV of mean inspiratory flow 0.642). The changes were less marked for EAdi. A positive noise limit was consistently found for flow and EAdi. Largest Lyapunov exponent and Kolmogorov-Sinai entropy for flow were greater during NAVA than PSV and increased with NAVA level ($P < 0.05$, partial η^2 0.334 and 0.312, respectively). Largest Lyapunov exponent and Kolmogorov-Sinai entropy for EAdi were not influenced by ventilator mode.

Conclusions: Compared with PSV, NAVA increases the breathing pattern variability and complexity of flow, whereas the complexity of EAdi is unchanged. Whether this improves clinical outcomes remains to be determined.

What We Already Know about This Topic

- Normal ventilation varies considerably from breath to breath, but this is lost with traditional positive pressure ventilation
- Neurally adjusted ventilatory assist (NAVA) uses diaphragmatic electromyography to trigger ventilation in a more natural manner

What This Article Tells Us That Is New

- In 12 intensive care patients, NAVA resulted in more complexity of airflow and breathing pattern compared with positive pressure ventilation
- NAVA may more closely mimic natural ventilation and thereby improve respiratory support

CONTRARY to controlled mechanical ventilation, modes of partial ventilatory assistance unload the respiratory muscles while preserving their spontaneous contractile activity.

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This, in theory, might help to prevent ventilator-induced diaphragm dysfunction,[1] but it also raises the issue of maintaining patient-ventilator synchrony.[2] The latter requires matching the timing of mechanical assistance to neural inspiration and inspiratory flow delivery to ventilatory demand. Failure to achieve patient-ventilator synchrony is associated with worsened sleep architecture,[3] increased duration of mechanical ventilation,[4] and, in extreme cases, the inability to discontinue ventilatory support.[5] In this regard, improving patient-ventilator synchrony has been among the main objectives of recently developed modes of partial ventilatory support.

Neurally adjusted ventilatory assist (NAVA)[6] is a mode of partial ventilatory support in which neural inspiratory activity is monitored through the continuous esophageal recording of the diaphragmatic electromyogram. Assistance is cycled on and off according to the time course of this signal and is delivered in proportion to its intensity. As a result, NAVA should intrinsically overcome important forms of patient-ventilator asynchrony, such as ineffective triggering and expiratory asynchrony, but also flow asynchrony.[2,7]

Depending directly on the central inspiratory activity, NAVA should result in a breathing pattern reflecting the natural variability observed in healthy adults.[8] Indeed, ventilation in normal human subjects is not monotonous but exhibits considerable breath-to-breath variability in discrete breathing pattern variables such as tidal volume (Vt), inspiratory time (Ti), and mean inspiratory flow (Vt/Ti).[9,10] The ventilatory activity is also nonlinear in nature and exhibits chaos-like mathematical complexity.[11,12] Ventilatory variability and complexity are influenced by several factors including the load–capacity relationship of the respiratory system,[13–15] vagal afferent traffic to the brain,[16] and the activity of the central pattern generators.[12] This is also true in critically ill patients during assisted mechanical ventilation[17] and during spontaneous breathing trials in the process of ventilator weaning.[18] In this latter setting, the variability of breathing has a prognosis value.[18]

In addition, recent data suggest that inputting some variability into mechanical ventilation might be beneficial.[19,20] Noisy ventilation has, thus, been shown to improve oxygenation in animal models of lung injury.[21–24] This is associated with a positive effect on respiratory mechanics—reduced mean inspiratory peak airway pressure and elastance—and with reduced histologic damage even in comparison with a tidal volume reduction strategy.[25]

Therefore, we reasoned that NAVA, because it directly links mechanical assistance to neural inspiratory activity, should result in greater breathing pattern variability and complexity compared with conventional ventilator modes. We also reasoned that because respiratory loading decreases the variability of breathing, increasing levels of NAVA should increase the breathing pattern variability and complexity.

To test these hypotheses, we studied respiratory variability and complexity in mechanically ventilated patients switched from pressure support ventilation (PSV) to progressively increasing levels of NAVA. In addition, to elucidate how the load–capacity relationship of the respiratory system contributes to the variability and complexity identified in the ventilatory flow signal, we analyzed the diaphragmatic electrical activity (EAdi) signal in the same manner as the ventilatory flow signal and compared their dynamics.

Materials and Methods

The study took place during a 5-month period (May 1, 2008, to September 30, 2008) in a 10-bed intensive care unit within a 2,000-bed university hospital. As an observational protocol, it was approved by the institutional review board of "Société de Pneumologie de Langue Française" (Paris, France). Informed consent was obtained from the patient or family member.

Patients

We analyzed the recordings obtained in patients in whom the treating physician decided to use NAVA during weaning from mechanical ventilation according to the clinical practice policy in place in the intensive care unit. Preconditions for the institution of NAVA included (1) poor clinical tolerance of PSV for at least 2 h when adjusted to provide a Vt of 6–8 ml/kg at a setting not exceeding 25 cm H_2O; this was decided by the clinician in charge of the patient—who was not involved in the research—either because of a direct indication by the patient that his or her breathing was a matter of discomfort or according to usual clinical criteria; (2) a Ramsay sedation scale score less than 4 in the absence of sedation for at least the preceding 12 h; (3) FIO_2 less than or equal to 50% and positive end-expiratory pressure less than or equal to 10 cm H_2O; (4) hemodynamic stability without vasopressor or inotropic medication; (5) estimated remaining duration of mechanical ventilation more than 48 h. The exclusion criteria were mainly related to the clinical contraindications to the use of NAVA. Individuals with known or suspected phrenic nerve dysfunction, other neuromuscular disorders that may adversely alter EAdi signal quality, impaired respiratory drive, contraindications to EAdi catheter placement (*e.g.*, gastroesophageal varices or obstruction, recent gastroesophageal surgery, facial surgery or trauma, or upper gastrointestinal bleeding), or clinical instability for any reason were excluded. Patients in whom the decision to withhold life-sustaining treatment had been made and pregnant women and those younger than 18 yr were also not considered. According to these criteria, 12 patients were evaluated. The clinical characteristics and indications for mechanical ventilation in the 12 patients are summarized in table 1. Male patients were intubated with an 8-mm internal diameter endotracheal or tracheostomy tube. In female patients, a 7.5-mm internal diameter endotracheal tube was used.

Protocol

Once the decision was made to initiate NAVA, the conventional nasogastric tube was removed and replaced with a

Table 1. Patient Characteristics at Enrollment

Patient	Gender (M/F)	Age (yr)	BMI (kg/m^2)	SAPS II	Admission Pathology	MV (d)	PSV (cm H_2O)	Vt, PSV (ml/kg)	FIO_2	PEEP (cm H_2O)
1	M	57	41	33	Septic shock, ALI	9	23	6.8	0.40	5
2	M	38	22	33	Septic shock, ALI	2	12	10.1	0.40	5
3	F	83	55	58	CHF	3	14	5.5	0.40	5
4	M	57	24	38	Septic shock, ALI	12	14	6.0	0.40	5
5	F	62	25	104	Severe malaria, ALI	7	18	8.7	0.35	5
6	M	68	25	87	Septic shock, ALI	2	6	7.4	0.40	5
7	M	43	28	64	Drug intoxication	7	15	6.1	0.40	5
8	M	78	39	66	Pneumonia, ALI	4	16	7.4	0.50	10
9	M	66	23	60	Pneumonia, ALI	3	12	7.1	0.40	4
10	M	68	26	35	Pneumonia, ALI	9	12	7.9	0.50	4
11	M	62	29	75	CHF	1	15	8.4	0.40	5
12	M	45	23	43	Septic shock, ALI	2	10	6.0	0.30	4
Mean		60.6	30.0	58.0		5.1	13.9	7.3	0.40	5.2
SEM		3.9	2.8	6.6		1.0	1.2	0.4	0.02	0.5

ALI = acute lung injury; BMI = body mass index; CHF = congestive heart failure; FIO_2 = inspired oxygen fraction; MV = mechanical ventilation; PEEP = positive end-expiratory pressure; PSV = inspiratory pressure support level above PEEP; SAPS II = Simplified Acute Physiology Score II; Vt, PSV = tidal volume during pressure support (ventilation expressed in milliliters per kilogram predicted body weight); SEM = standard error of the mean.

16-Fr EAdi catheter (Maquet Critical Care, Solna, Sweden). After a period of stabilization on PSV once the EAdi catheter was properly positioned, an initial 10-min recording was performed. The ventilator mode was then switched to NAVA (Servo-i, Maquet Critical Care) with a gain factor of 1 to 4 ($NAVA_1$, $NAVA_2$, $NAVA_3$, and $NAVA_4$). NAVA level is a proportional gain factor expressed in centimeters of water over microvolt of EAdi. It represents the magnitude (in centimeters of water) of positive airway pressure applied per microvolt of EAdi during the course of each inspiration.

At each NAVA level, 10 min of stabilization were allowed before 10-min recordings were obtained. FIO_2 and positive end-expiratory pressure were kept constant. The pneumatic and EAdi triggers had each been adjusted previously by the treating physicians to be as sensitive as possible without autotriggering.

Data Acquisition

In each condition, airway pressure, flow, and EAdi were acquired at 100 Hz from the ventilator *via* a RS232 interface connected to a computer using commercially available software (Servo-i RCR, Version 2, Maquet Critical Care). Observer graded scores of general comfort in ventilated patients using a previously validated scale (adaptation to the intensive care environment score)[26] were obtained by the same study investigator at the end of each condition. Samples for arterial blood gas analysis were drawn at this time as well.

Data Analysis

Breath-by-Breath Variability. Flow-derived breathing pattern parameters were determined on a breath-by-breath basis for each of the five conditions as described under Protocol in Materials and Methods. These included tidal volume (Vt), neural respiratory rate, minute ventilation, duration of inspiration (Ti), expiration, total respiratory cycle (Tt), inspiratory duty cycle (Ti/Tt), and mean inspiratory flow (Vt/Ti). For EAdi, peak ($EAdi_{peak}$), rate of rise (peak value divided by time to peak of EAdi) ($EAdi_{peak}/EAdi_{tp}$), and integrated EAdi activity relative to the end-expiratory baseline value ($\int$EAdi) were also computed on a breath-by-breath basis. The coefficient of variation (CV; SD divided by the mean) and autocorrelation descriptors (number of significantly correlated breaths or lag; autocorrelation coefficient between the first and second breaths or r-lag^{-1}) for both flow and EAdi related variables were then calculated using a software routine developed for Matlab (Mathworks, Natick, MA). Peak (P_{peak}) and mean inspiratory airway pressure (P_{mean}) were also obtained and included positive end-expiratory pressure.

Ventilatory Complexity: Noise Titration. After subsampling the signal at 5 Hz, the noise titration procedure[27] was performed as described previously[11,12,17,28] (see detailed description in Supplemental Digital Content 1, http://links.lww.com/ALN/A571). In brief, this technique first ascertains the presence of nonlinearity in the signal through a statistical process, and then it quantifies the amount of added white noise needed to mask this nonlinearity. A noise limit above 0 means nonlinearity and a certain degree of chaos-compatible complexity.[27] It allows the safe use and interpretation of traditional nonlinear descriptors that are all sensitive to noise (see next paragraph).

Ventilatory Complexity: Sensitivity to Initial Conditions and System Unpredictability. Various characteristics of a complex dynamical system are useful for their description. These include their sensitivity to initial conditions, or, in other words, how perturbations occurring in the past affect the future behavior of the system. Characteristically, small differences in the starting state of the system can lead to enormous differences in its final state as the result of an exponential growth of error. This happens even though the

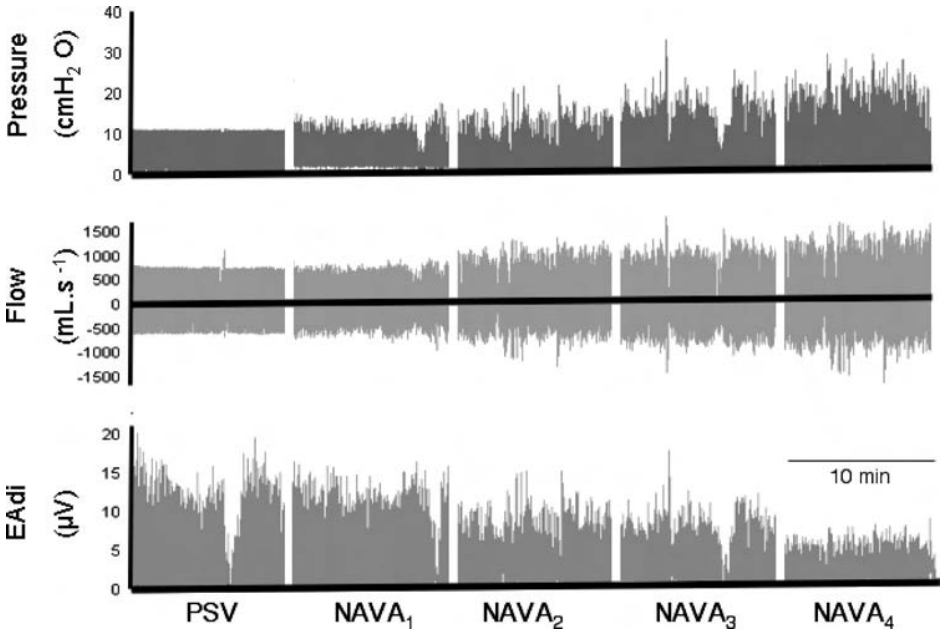

Fig. 1. Continuous 10-min recordings of airway pressure, flow, and diaphragm electrical activity (EAdi) during pressure support ventilation (PSV) and various levels of neurally adjusted ventilatory assist (NAVA) in one patient (patient 12). Noticeable variation in airway pressure and flow develops when changing mode from PSV to NAVA, which increases further as NAVA gain is raised from 1 to 4 cm $H_2O/\mu V$ EAdi ($NAVA_{1,2,3,4}$). EAdi decreases in magnitude with increasing NAVA gain with little apparent change in breath-to-breath variation.

considered system is deterministic, namely that it is driven by a mechanism that does not involve random elements. We quantified the sensitivity to initial conditions for flow and EAdi using the largest Lyapunov exponent (LLE)[29] (Dataplore v 2.0.9, Datan, Teltow, Germany), which increases as the system is more sensitive to initial conditions. Another characteristic of a complex system is how unpredictable it is. This can be estimated by calculating the Kolmogorov-Sinai Entropy (KSE),[30] as the sum of the positive Lyapunov exponents.[12] A low value of KSE indicates predictability and regularity, whereas a high value denotes unpredictable and random variations.[30]

Three-dimensional phase portraits of the flow and Edi signals were also determined. The phase space of a dynamical system is the multidimensional space in which all the possible states of the system are represented. The phase portrait of a periodical system is a simple closed loop, whereas the phase portrait of a chaotic system is a complicated set of nonrepeating patterns.

Statistical Analysis

Results are expressed as mean values ± SEM. Statistical analysis was performed with Prism 4.0a software (GraphPad Software, San Diego, CA). Distribution being normal (Shapiro-Wilk test), comparisons between the five conditions were performed with one-way analysis of variance for repeated measures, followed, when indicated, by pairwise comparisons using Tukey *post hoc* test. Correlations between continuous variables were examined with Pearson correlation when the distribution was normal (Shapiro-Wilk test) and with Spearman correlation when the distribution wan not normal, depending on the distribution. Differences were considered significant when $P < 0.05$. Effect size was estimated through the calculation of the partial η^2 using PASW Statistics 18 (Chicago, IL).

Results

Figure 1 shows an example (patient 12) of the pressure, flow, and EAdi signals during the five conditions. Group mean values for representative breathing pattern variables are provided in figure 2 (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571). Switching from PSV to $NAVA_1$ did not seem to significantly modify the pattern of breathing (fig. 2). Increasing the level of NAVA assistance had no significant effect on breathing frequency and the inspiratory duty cycle (Ti/Tt), but it did produce significant increases in Vt ($P < 0.05$, partial $\eta^2 = 0.394$) and Vt/Ti ($P < 0.05$, partial $\eta^2 = 0.429$) when $NAVA_3$ and $NAVA_4$ were reached (fig. 2). Minute ventilation paralleled the changes in Vt (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571). Ti was significantly shorter under $NAVA_4$ in comparison with PSV (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571).

Similarly, the indices of EAdi activity were not significantly different between PSV and $NAVA_1$ (fig. 3). Increasing the NAVA level resulted in a progressive decrease of $EAdi_{peak}$, $EAdi_{peak}/EAdi_{tp}$, and $\int EAdi$. $EAdi_{peak}$ and $EAdi_{peak}/EAdi_{tp}$ were significantly lower in $NAVA_4$ than in both PSV and $NAVA_1$ ($P < 0.05$, partial $\eta^2 = 0.399$ and 0.367, respectively), whereas $\int EAdi$ was significantly lower in $NAVA_4$ than in $NAVA_1$ ($P < 0.05$) (fig. 3) (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571).

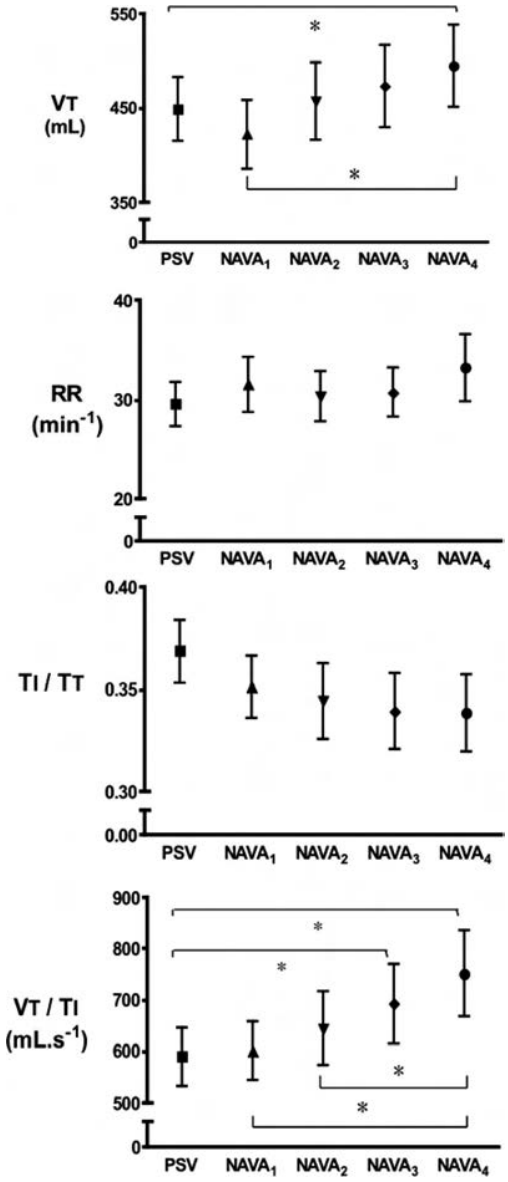

Fig. 2. Effects of ventilator mode and level of assistance on representative breathing pattern variables. Compared with pressure support ventilation (PSV), the most noticeable difference is the increase in mean inspiratory flow (Vt/Ti) as the neurally adjusted ventilatory assist (NAVA) gain is raised stepwise from 1 to 4 cm $H_2O/\mu V$ diaphragm electrical activity ($NAVA_{1,2,3,4}$). There is no significant change in respiratory rate (RR) or inspiratory duty cycle (Ti/Tt). Tidal volume (Vt) differs significantly at the highest NAVA gain ($NAVA_4$). Data are means ± SEM; $^*P < 0.05$.

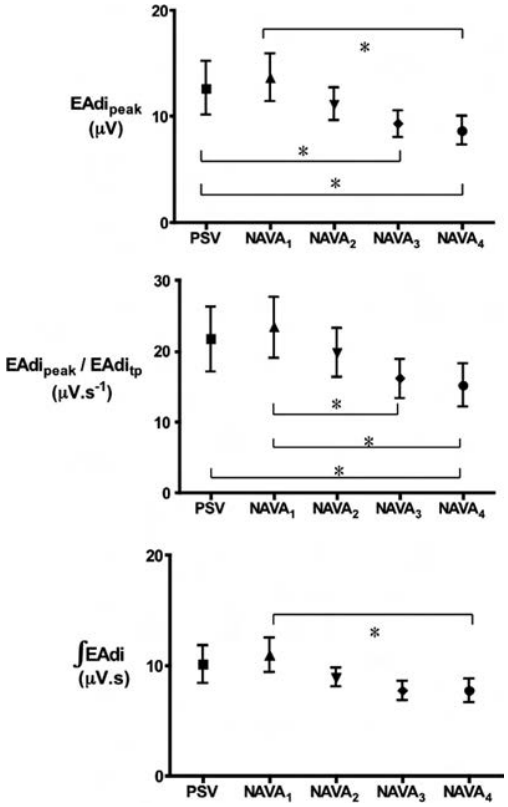

Fig. 3. Effects of ventilator mode and level of assistance on diaphragmatic electrical activity (EAdi). Peak ($EAdi_{peak}$), rate of rise ($EAdi_{peak}/EAdi_{tp}$), and integrated EAdi per breath (∫EAdi) are similar during pressure support ventilation (PSV) and the lowest level of neurally adjusted ventilatory assist (NAVA). EAdi indices decrease progressively as NAVA gain increases from 1 to 4 cm $H_2O/\mu V$ EAdi ($NAVA_{1,2,3,4}$). Data are means ± SEM; $^*P < 0.05$.

The switch from PSV to $NAVA_1$ and further increases in NAVA level had no impact on Pa_{O_2}/FiO_2 (table 2). However, Pa_{CO_2} was slightly lower and arterial pH somewhat higher during $NAVA_4$ compared with $NAVA_1$ ($P < 0.05$) (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571).

Switching from PSV to $NAVA_1$ did not result in a significant change in P_{peak} or P_{mean} (fig. 4). P_{peak} particularly but also P_{mean} rose as the NAVA gain was increased. For $NAVA_3$ and $NAVA_4$, P_{peak} was higher than during PSV and $NAVA_1$ ($P < 0.05$). P_{mean} was higher for $NAVA_4$ than $NAVA_1$ (fig. 4) (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571).

No significant change in the adaptation to the intensive care environment score was detected (see Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/A571).

Breath-by-Breath Variability

A significant increase in the CV of Vt/Ti ($P < 0.05$, partial $\eta^2 = 0.642$) was immediately apparent during $NAVA_1$ when compared with PSV (fig. 5). Increasing the level of NAVA produced an increase in the breath-by-breath variability of most of the breathing pattern variables (fig. 5) (see Supplemental Digital Content 1, table 2, http://links.lww.com/ALN/A571). For these variables, the CV was significantly higher in $NAVA_4$ than in both PSV and $NAVA_1$. The autocorrelation analysis showed similar trends, but the changes were significant only for Vt/Ti and, to a lesser extent, for respiratory rate. Indeed, the lag of Vt/Ti was lower in $NAVA_4$ than in both PSV and $NAVA_1$ ($P < 0.055$, partial $\eta^2 = 0.356$). The autocorrelation coefficient of Vt/Ti and of respiratory rate was lower in $NAVA_4$ than in $NAVA_1$ ($P < 0.05$).

Table 2. Arterial Blood Gas Analysis during Pressure Support Ventilation and at Various Levels of NAVA

Arterial Blood Gases	PSV	$NAVA_1$	$NAVA_2$	$NAVA_3$	$NAVA_4$
pH	7.38 ± 0.02	7.37 ± 0.03*	7.38 ± 0.03	7.39 ± 0.02	7.40 ± 0.02†
Pa_{O_2}/F_{IO_2}	202 ± 18	203 ± 18	212 ± 20	198 ± 12	207 ± 15
Pa_{CO_2} (mmHg)	40.9 ± 2.9	42.2 ± 2.9*	40.5 ± 2.9	40.4 ± 2.7	38.9 ± 2.6

Data provided as mean ± standard error of the mean.

* $P < 0.05$ *versus* $NAVA_4$. † $P < 0.05$ *versus* PSV.

F_{IO_2} = inspired oxygen fraction; $NAVA_{1,2,3,4}$ = neurally adjusted ventilatory assist with a gain of 1, 2, 3, and 4 cm $H_2O/\mu V$ diaphragmatic electrical activity; Pa_{O_2} = partial pressure of alveolar oxygen; Pa_{CO_2} = arterial carbon dioxide tension; PSV = pressure support ventilation.

The CV of $EAdi_{peak}$, $EAdi_{peak}/EAdi_{tp}$, and ∫EAdi did not significantly increase when PSV was switched to $NAVA_1$ (fig. 6). Increasing the NAVA gain had a limited effect on the CV for these three EAdi variables until the highest level of assistance was reached. The CV of $EAdi_{peak}/EAdi_{tp}$ was higher in $NAVA_4$ than in all other conditions ($P < 0.05$, partial $\eta^2 = 0.365$), whereas the CV of the $EAdi_{peak}$ was higher in $NAVA_4$ than in $NAVA_1$ ($P < 0.05$, partial $\eta^2 = 0.191$). The lag and the autocorrelation coefficient for $EAdi_{peak}$, $EAdi_{peak}/EAdi_{tp}$, and ∫EAdi were not significantly altered by the change in ventilator mode or the subsequent increases in NAVA level (fig. 6) (see Supplemental Digital Content 1, table 3, http://links.lww.com/ALN/A571).

Ventilatory Complexity

A positive noise limit was obtained with the noise titration procedure in all patients for both the flow and EAdi signals during PSV and all levels of NAVA, consistently indicating the presence of a nonlinear chaotic system. In all patients and in all conditions for both flow and EAdi, at least one of the Lyapunov exponents was positive, at least one was negative, and their sum was negative, a pattern in keeping with chaos. The LLE for ventilatory flow was higher for $NAVA_2$, $NAVA_3$, and $NAVA_4$ than PSV ($P < 0.05$, partial $\eta^2 = 0.334$) (fig. 7). The same pattern was observed for KSE ($P < 0.05$, partial $\eta^2 = 0.312$) (see Supplemental Digital Content 1, table 4, http://links.lww.com/ALN/A571). In contrast, switching from PSV to NAVA and then increasing NAVA gain had no effect on the LLE and KSE of the EAdi signal (fig. 7).

Figure 8A illustrates the difference between flow and EAdi complexity (fig. 8B) and the differential effects of increasing NAVA on this complexity, using three-dimensional phase portraits (example in patient 2). During PSV, the number of flow trajectories seems limited, describing a well-identifiable geometric pattern that is relatively simple. The phase portrait becomes less "geometrical" in $NAVA_1$, and the trajectories become more numerous and more tangled as NAVA increases. This phenomenon is much less apparent for the EAdi signal, where the phase portrait under PSV is already rather "complicated" (and more so than the flow phase portrait), and increasing NAVA does not radically change the overall shape. Although low, significant correlations were found between some of the breathing pattern variables and the indices of the complexity of ventilatory flow (see Supplemental Digital Content 1, table 5, http://links.lww.com/ALN/A571). There was no such correlation for the EAdi signal.

Discussion

This study demonstrates that, in acutely ill mechanically ventilated patients, switching the mode of ventilatory assistance from PSV to NAVA and then increasing the support provided by NAVA is associated with increased variability of the pattern of breathing (fig. 5). This is also associated with greater complexity of the ventilatory flow signal (fig. 8), as evidenced by the significant increases in LLE and KSE (fig. 7). In contrast, the breath-to-breath variability and complexity of EAdi that seems more marked than their ventila-

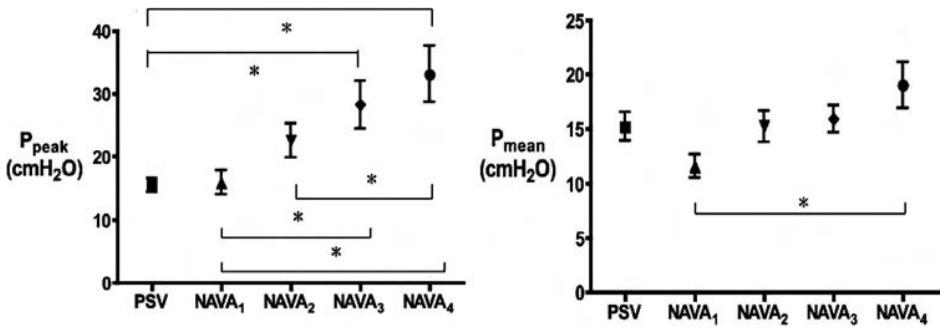

Fig. 4. Effects of ventilator mode and level of assistance on peak (P_{peak}) and mean inspiratory airway pressure (P_{MEAN}). P_{peak} is similar and P_{MEAN} slightly lower when ventilator mode changes from pressure support ventilation (PSV) to neurally adjusted ventilatory assist (NAVA). Both P_{peak} and P_{mean} rise as NAVA gain increases from 1 to 4 cm $H_2O/\mu V$ diaphragm electrical activity ($NAVA_{1,2,3,4}$). Data are means ± SEM; *$P < 0.05$.

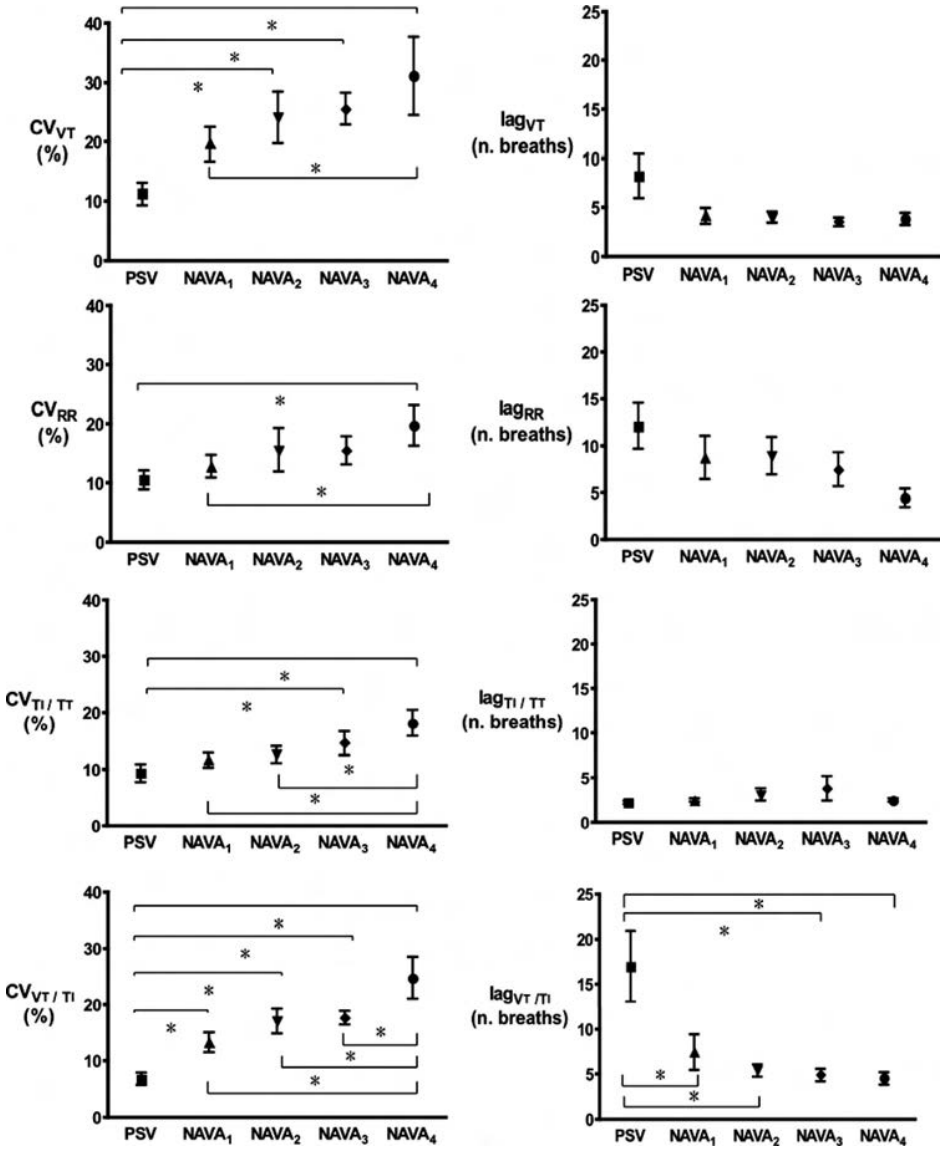

Fig. 5. Effects of ventilator mode and level of assistance on the coefficient of variation (CV) and autocorrelation analysis for representative breathing pattern variables. Compared with PSV, values for the CV are somewhat greater during NAVA and rise further as the gain increases from 1 to 4 cm $H_2O/\mu V$ diaphragm electrical activity. Autocorrelation analysis is used here to determine the number of breaths through which a significant correlation or lag is found. Considered an index of "short term memory," the greater the numerical value of lag, the larger the duration of interbreath correlation. With the exception of mean inspiratory flow, lag seems to be lower during NAVA. Overall, these results are consistent with increased breathing pattern variability during NAVA when compared with PSV. CV = coefficient of variation; CV_{RR} = CV of respiratory rate; CV_{Vt} = CV of tidal volume; $CV_{Ti/Tt}$ = CV of the inspiratory duty cycle; $CV_{Vt/Ti}$ = CV of mean inspiratory flow; lag = number of breaths among which a significant correlation was found; lag_{Vt} = lag of tidal volume; lag_{RR} = lag of respiratory rate; lag_{Vt} = lag of the tidal volume; $lag_{Ti/Tt}$ = lag of the inspiratory duty cycle; $lag_{Vt/Ti}$ = lag of mean inspiratory; $NAVA_{1,2,3,4}$ = neurally adjusted ventilatory assist with a gain of 1, 2, 3, 4 cm $H_2O/\mu V$ diaphragm electrical activity flow; PSV = pressure support ventilation. Data are means ± SEM; $^*P < 0.05$.

tory flow counterparts during PSV (figs. 5–7) are much less or not appreciably influenced by NAVA.

Breath-to-Breath Variability

Fluctuations in the resting breathing pattern of humans have long been known[31,32] and depend on various factors. Breathing pattern variability decreases during sleep and coma,[33,34] indirectly indicating the likely influence of ventilatory drive and/or respiratory afferent activity. In awake normal humans, breath-to-breath variability tends to decrease and autocorrelation tends to increase in response to mechanical loading,[13,14] a situation generally associated with modest changes in the central drive to breathe.[35,36] During weaning from mechanical ventilation, an inverse relationship between the breath-to-breath variability of Vt/Ti and dynamic compliance of the respiratory system has been reported.[18] The load–capacity relationship of the respiratory system, therefore, seems to be a major determinant of breath-to-breath variability: the higher the loading, the lower the variability. This is sup-

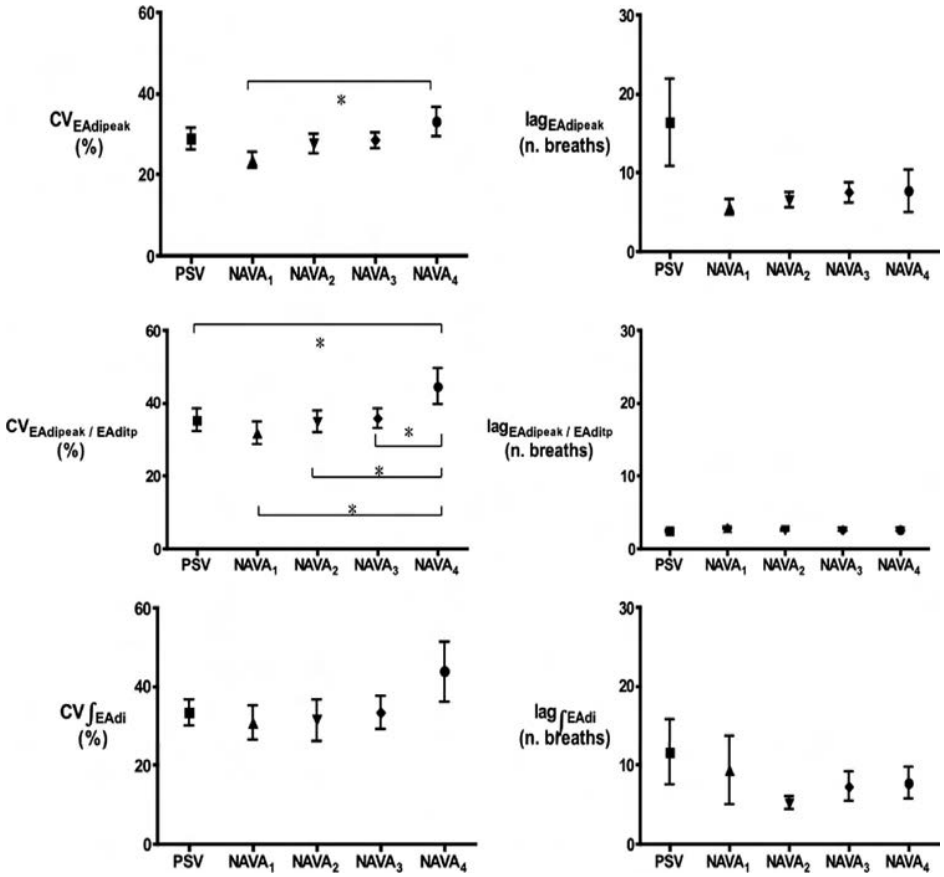

Fig. 6. Effects of ventilator mode and level of assistance on the coefficient of variation (CV) and autocorrelation analysis of diaphragm electrical activity (EAdi). The CVs for peak ($CV_{EAdipeak}$), rate of rise ($CV_{EAdipeak/EAditp}$), and integrated EAdi per breath ($CV_{\int EAdi}$) are similar between pressure support ventilation (PSV) and the lowest level of neurally adjusted ventilatory assist (NAVA). Increasing NAVA gain had a limited effect on these indices, values differing only at the highest NAVA setting. Values of lag, that is, the number of breaths among which a significant correlation is found by autocorrelation analysis, for peak ($lag_{EAdipeak}$), rate of rise ($lag_{EAdipeak/EAditp}$), and integrated Edi per breath ($lag_{\int EAdi}$) are not significantly altered by the change in ventilator mode or the subsequent increases in NAVA gain. $NAVA_{1, 2, 3, 4}$ = neurally adjusted ventilatory assist with a gain of 1, 2, 3, 4 cm $H_2O/\mu V$ EAdi, respectively. Data are means ± SEM; $^*P < 0.05$.

ported by our data. Indeed, we observed that such variability significantly increases with increasing levels of NAVA, namely during progressive unloading of the respiratory system (fig. 5). Respiratory unloading with NAVA also decreased the degree of autocorrelation, but in a much less marked manner (fig. 5). This can probably be taken as an indication that variability and autocorrelation are not measures of the same thing. Of note, the increased breath-to-breath variability that we observed was not accompanied by significant change in Vt, Vt/kg of predicted body weight and P_{mean}, supporting the idea that NAVA has the intrinsic potential to limit the risk of overassistance through the down-regulation of EAdi that is induced by the increase in assistance. This differs from PSV and is consistent with previous reports from other groups.[7,37,38]

Impact of Neuromechanical Coupling on Breathing Pattern Variability

As mentioned in the introduction, breathing pattern variability seems to depend on several factors that include ventilatory drive and the degree of mechanical loading imposed on the respiratory system. To date, human respiratory variability has been studied only through the analysis of the mechanical output of the ventilatory command (*i.e.*, flow, volume, or thoracoabdominal displacement), including with NAVA where data reporting coefficients of variation of Vt are available.[7,37] This does not necessarily provide an accurate picture of the respiratory controllers, however, because the underlying behavior of central respiratory neural output can be substantially altered by the mechanical characteristics of the respiratory system.

The current study overcomes this limitation by using for this analysis, seemingly for the first time, measurements of EAdi that directly reflect central respiratory neural output. These data indicate that the increase in breath-to-breath variability of ventilatory flow observed during NAVA is in fact due to "unmasking" of the underlying variability in central respiratory neural output and a direct result of the improvement in neuromechanical coupling. Indeed, contrary to the variability in breathing pattern variables, the breath-to-breath variability of EAdi was similar during PSV and NAVA and did not increase with the NAVA level (except for $NAVA_4$). In addition, right angles were observed in three-

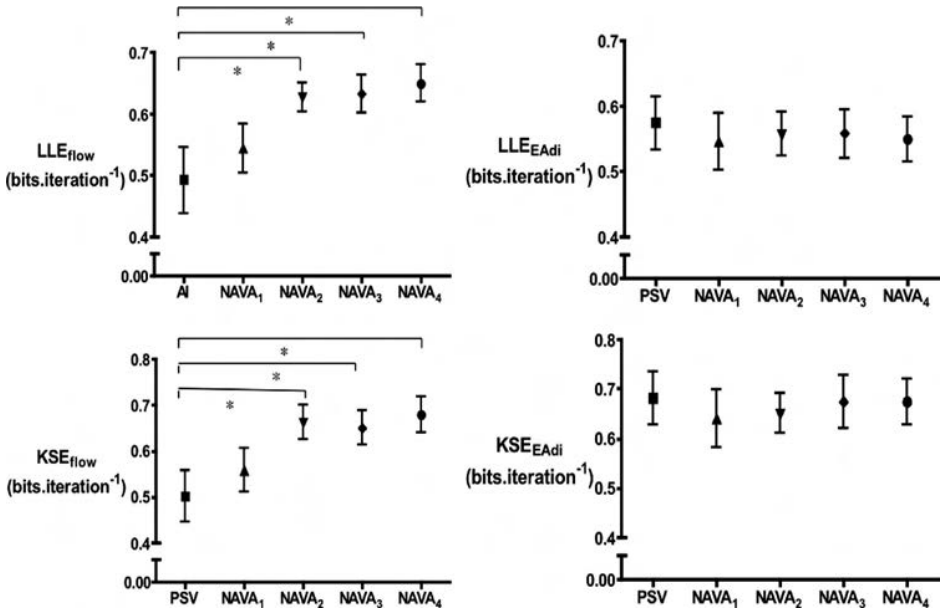

Fig. 7. Effects of ventilator mode and level of assistance on indices quantifying the sensitivity to initial conditions (largest Lyapunov exponent [LLE]) and the unpredictability (Kolmogorov-Sinai entropy [KSE]) of ventilatory flow and diaphragm electrical activity (EAdi). LLE for flow rises when changing the ventilator mode from pressure support ventilation (PSV) to neurally adjusted ventilatory assist (NAVA) and then increasing the gain from 1 to 2 cm $H_2O/\mu V$ Edi ($NAVA_1$, $NAVA_2$). No further increase in LLE flow occurs at the higher gain levels ($NAVA_3$ and $NAVA_4$). In contrast, both LLE and KSE for EAdi are no different between PSV and NAVA and are not altered by increasing NAVA gain. Data are means ± SEM; $^*P < 0.05$.

dimensional phase portraits of flow but not of EAdi (see fig. 8). The absence of right angle trajectories being one of the characteristics of deterministic dynamics reinforces the hypothesis that EAdi might be the most accurate index of intrinsic complexity, whereas flow is influenced by respiratory system mechanics. Therefore, we submit that NAVA-related unloading reveals, in terms of breathing pattern, the underlying variational activity in central respiratory neural output that is itself not particularly sensitive to the mechanical load.

Respiratory Complexity

As in previous studies conducted in this field by our group,[11,12,17,28] we carried out complexity analyses on continuous oscillatory signals (here flow and EAdi), as opposed to a time series of discrete values. To our knowledge, this is one of the few studies to analyze the breathing pattern complexity in mechanically ventilated patients. With this approach, consecutive breaths are described in terms of an ensemble of signal trajectories (fig. 8). If only one trajectory is possible, as in a truly periodic system,[39] complexity is minimal, and all breaths should be identical. This is the case during assist-control mechanical ventilation in passive patients[17] where ventilatory flow is driven solely by the ventilator clock. If, conversely, several trajectories are possible, a given breath can differ from the previous or the following one. The more numerous the trajectories (in other words, the more complex the system), theoretically the more marked the interbreath differences can be (and the less likely autocorrelation). In this view, one expects some similarity between the evolution of breath-to-breath variability ("downstream" point of view) and the evolution of complexity ("upstream" point of view) in response to a given intervention. This is indeed what we observed: both the variability in the breathing pattern and the complexity of ventilatory flow were low during PSV (figs. 7 and 8), became greater with the change to NAVA, and further increased as the NAVA gain increased. Although weak in strength, significant correlations existed between the indices of ventilatory complexity and breathing pattern variability (see Supplemental Digital Content 1, table 5, http://links.lww.com/ALN/A571). Therefore, our data indicate that breath-to-breath variability depends, at least in part, on the underlying complexity of the central ventilatory command.

In striking contrast to what was observed with the ventilatory signal, the variability and the complexity of the EAdi signal—that were already relatively high during PSV, and comparatively higher than that of the flow signal—remained largely unaffected by the change in ventilator mode to NAVA and the increase in assistance with higher NAVA gain. Therefore, NAVA seems to allow the variability and complexity of the central respiratory activity to translate into their ventilatory flow counterparts. This suggests that the variability and complexity of ventilatory flow are related not only to the load–capacity balance of the respiratory system[18] but also to the neural activity of the respiratory controller. Practically speaking, assessing ventilatory flow variability and complexity could provide a simple means to monitor the respiratory neuromechanical coupling, or load–capacity balance, over time. The variability and complexity analysis performed on the EAdi signal would provide information more

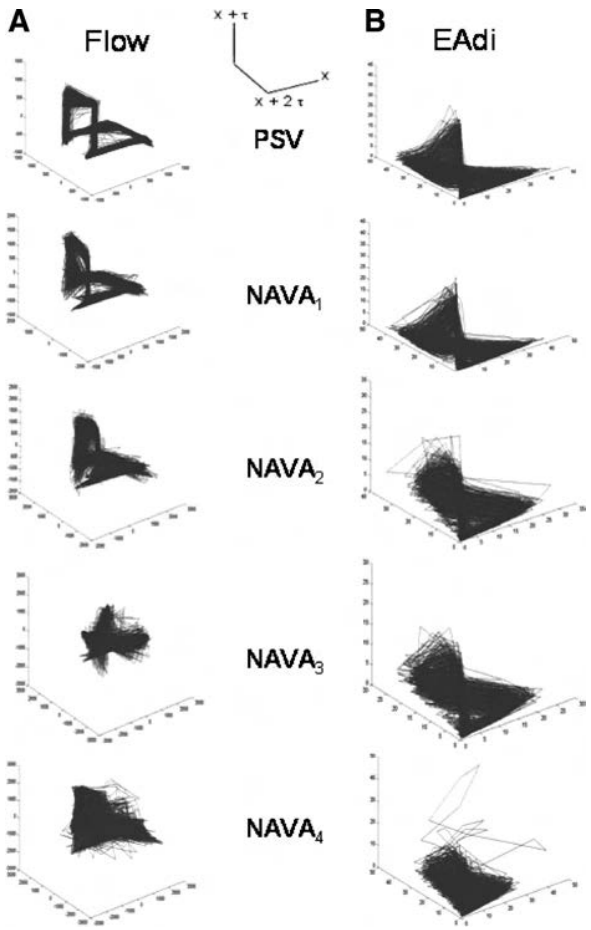

Fig. 8. Three-dimensional phase portraits of flow (*A*) and diaphragm electrical activity (EAdi) (*B*) during pressure support ventilation (PSV) and at increasing levels of neurally adjusted ventilatory assist ($NAVA_{1,2,3,4}$) in one patient (patient 2). Insert identifies the dimensional axes: x, $x + t$, and $x + 2t$, where x indicates the values of flow or Edi obtained during continuous 10-min recordings for each condition and t represents the time delay derived as indicated by Takens (Reference 9 in Supplemental Digital Content 1, http://links.lww.com/ALN/A571). The number of flow trajectories (*A*) seems limited during PSV, describing a well-identifiable geometric pattern that is relatively simple. The phase portrait becomes less geometrical when the ventilator mode is changed to the lowest NAVA setting ($NAVA_1$). Thereafter, the trajectories become more numerous and more tangled as the NAVA gain increases. This phenomenon is much less apparent for the EAdi signal (*B*), where the phase portrait during PSV is already rather complicated (in fact, more so than the flow phase portrait). Moreover, increasing the NAVA gain does not radically change the overall shape.

purely related to the intrinsic neural activity of the respiratory controller.

Study Limitations

Because of the observational design of the study, we examined only a single level of PSV. Therefore, we cannot rule out the hypothesis that progressively increasing PSV would similarly increase breath-to-breath variability by either reducing the mechanical load or altering the respiratory drive. Nevertheless, switching from PSV to $NAVA_1$ increased the CV of Vt and Vt/Ti and decreased the Vt/Ti autocorrelation (fig. 5), while there was no significant change in Vt and breathing frequency (fig. 2). This suggests a specific effect of NAVA on variability, all the more so that the patients may have been somewhat underassisted during $NAVA_1$ (as reflected by trends in P_{MEAN} [fig. 4] and EAdi [fig. 3]). By contrast, $NAVA_4$ could have corresponded to some degree of overassistance, because it was associated with a tendency of variability to reincrease after a sort of a plateau (significant for Vt/Ti, fig. 5).[37]

Also, because the study was observational, there was by definition no randomization of the NAVA levels studied, which is another theoretical limitation of the study. According to the standard clinical practice procedure when attempting to titrate a therapeutic intervention, NAVA was increased in a progressive manner to find the optimal balance between respiratory muscle unloading and overassitance, as reported previously in patients.[7,37] Therefore, we cannot rule out the existence of some degree of "sequence" bias. Note that the recordings, however, were not performed immediately after the setting changes, but after 10 min of stabilization.

Finally, in the current study, most patients were studied while they were recovering from an acute lung injury and not during the most acute phase, and so our data apply to moderate acute lung injury.

Of note, the fact that inspiration results from the cooperation between the diaphragm and other respiratory muscles (ribcage muscles, scalenes, and sternomastoids) while NAVA is driven by EAdi alone could contribute to the higher variability observed with NAVA.

Clinical Perspectives

We did not observe a dramatic clinical change after switching from PSV to NAVA in this group of patients, and there was no obvious clinical indication that the stepwise increase in NAVA provided what could have been termed an optimal level of ventilatory support (*e.g.*, no improvement in the adaptation to the intensive care environment score with increasing levels of NAVA). However, the study population is very small, and the experimental protocol was not designed or powered to examine the effects of NAVA on clinical outcomes. Yet, NAVA did increase the respiratory variability and complexity. This is a rationale to design studies examining the impact of NAVA on clinical outcomes known to be associated with greater variability.[19,20]

NAVA is not the only ventilatory mode that increases the variability of breathing. Noisy ventilation that delivers a Vt with up to 40% CV is a ventilatory mode designed to purposely increase the variability of breathing. Animal studies have shown the benefits of this approach on gas exchange, respiratory mechanics, and lung structure during lung injury.[19,21–23,25] Even though human data are currently not available, these observations lend support to the notion that an increased respiratory variability might be a good thing during mechanical ventilation. Proportional assist mechanical ventilation relies on the dynam-

ical adaptation of the ventilatory support to the mechanics of the respiratory system and its fluctuations. The proportional assist mechanical ventilation-induced mechanical unloading of the respiratory system is associated with increased breathing pattern variability[40] in a manner that resembles our observations with NAVA. In our patients, increasing the level of NAVA support produced an increase in ventilatory flow variability, whereas it did not affect the variability of the diaphragm electromyogram that seemed to be high to begin with. In our view, this indicates that NAVA improved the neuromechanical coupling of the respiratory system. Studying the effects of proportional assist mechanical ventilation on the variability of diaphragmatic electromyogram would, thus, provide an interesting way of comparing it to NAVA.

In clinical practice, whether variability is distinctive of patient-ventilator interaction and whether monitoring respiratory variability and/or complexity is an appropriate means to assess this interaction in the clinical setting will have to be studied.

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Neurally Adjusted Ventilatory Assist Increases Respiratory Variability and Complexity in Acute Respiratory Failure

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SUPPLEMENTAL DIGITAL CONTENT 1

DETAILED METHODS

Data Analysis

Ventilatory complexity: noise titration. Flow and EAdi signals were first subsampled at 5 Hz, a frequency considered to provide an adequate compromise between oversampling —that carries the risk of introducing artefactual linearities in the data and thus to make the detection of nonlinearities falsely fail— and undersampling that carries the risk of aliasing—[1, 2]. The noise titration procedure [3] was then performed as previously described [2,4-6]. This method first involves the simulation of families of linear and nonlinear polynomial autoregressive models with varying memory and dynamical order using the Volterra-Wiener method [1]. The best linear and nonlinear models are chosen according to the minimal information theoretic criterion, and subsequently the null hypothesis (best linear model) is tested against the alternate hypothesis (best nonlinear model) using parametric (F-test) and nonparametric (Mann-Whitney) statistics. The algorithm is used according to a trial-and-error process including the testing of K (embedding dimension) values of 4 to 6 and nonlinear degrees of 3 to 5. Nonlinearity is ascertained if the null hypothesis is rejected, namely if a nonlinear model best describes the data. A "noise limit" is then calculated as the amount of added white noise needed to mask the nonlinearity of the original signal. By

definition therefore, a noise limit above zero indicates that the considered set of data contains nonlinearities and features a certain degree of complexity —that can be called chaos in the case of a deterministic process. Noise limit changes from one state of the system to another state then bear witness of variations in its complexity provided that the signal-to-noise ratio remains constant. A system with a positive noise limit can adequately be characterized using traditional descriptors quantifying the sensitivity to initial conditions and unpredictability[3]. Conversely, if the noise limit = 0 nonlinearity is not detected. This indicates that either the time series is not nonlinear or that the complex component of the signal has already been neutralized by the background noise within the data [3].

Ventilatory complexity: sensitivity to initial conditions and system unpredictability. Complex dynamical systems are sensitive to initial conditions, and exhibit an exponential divergence in the phase space. This can be quantified by deriving the spectrum of Lyapunov exponents and determining the largest Lyapunov exponent. In the present study, the largest Lyapunov exponent was calculated for flow and EAdi using the polynomial interpolation approach described by Briggs [4,7] (Dataplore v 2.0.9, Datan, Teltow, Germany). The higher the largest Lyapunov exponent, the more sensitive the system to initial conditions. The degree of predictability of a complex chaotic system can be estimated by Kolmogorov-Sinai entropy. Kolmogorov-Sinai entropy measures the amount of regularity and is defined as the divergence of nearby points within the phase space (see discussion of three-dimensional phase portraits below). Kolmogorov-Sinai entropy was calculated as the sum of the positive Lyapunov exponents [4] for flow and EAdi (Dataplore v 2.0.9, Datan, Teltow, Germany). A low value of Kolmogorov-Sinai entropy indicates predictability and regularity, whereas a high value denotes unpredictable and random variation [8].

Three-dimensional phase portraits of the flow and Edi signals were also determined. The phase space of a dynamical system is the multidimensional space in which all the possible states of the system are represented. Every degree of freedom of the system defines an axis of this space, and each possible state of the system corresponds to one unique point. A succession of such plotted points is analogous to the system's state evolving over time and defines a trajectory. The phase portrait of a periodical system is a simple closed loop, whereas the phase portrait of a chaotic system is a complicated set of nonrepeating patterns, which is, however, confined in a finite zone of the phase space (which accounts for the deterministic nature of chaos). For our purposes, the phase portraits corresponding to each condition were constructed in three dimensions, corresponding for each value x of ventilatory flow or EAdi to x, $x+$ t, and $x+$ 2t according to the embedding theorem formulated by Takens [9].

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Table 1. Breathing Pattern, Diaphragm Electrical Activity (EAdi), and Comfort Scores during Pressure Support Ventilation and at Various Levels of NAVA

	PSV	**$NAVA_1$**	**$NAVA_2$**	**$NAVA_3$**	**$NAVA_4$**
Breathing pattern					
V_T (ml)	448 ± 34	422 ± 37†	457 ± 41	473 ± 43	495 ± 44 *
V_T/kg (ml/kg)	7.3 ± 0.5	6.8 ± 0.5 †	7.4 ± 0.6	7.7 ± 0.6	8.1 ± 0.7 *
RR (breath/min)	29 ± 2	31 ± 3	31 ± 3	31 ± 2	33 ± 4
V'_E (l/min)	12.9 ± 1.2	12.5 ± 1.1†	13.1 ± 1.5 †	13.9 ± 1.6	15.3 ± 1.9*
T_I (sec)	0.80 ± 0.06	0.71 ± 0.06	0.72 ± 0.05	0.71 ± 0.05	0.67 ± 0.05*
T_E (sec)	1.4 ± 0.2	1.4 ± 0.2	1.5 ± 0.2	1.5 ± 0.2	1.4 ± 0.2
T_T (sec)	2.2 ± 0.2	2.1 ± 0.2	2.2 ± 0.2	2.2 ± 0.2	2.1 ± 0.2
T_I / T_T (%)	37 ± 16	35 ± 15	34 ± 19	34 ± 19	34 ± 19
V_T/T_I (ml/sec)	590 ± 57	600 ± 57†	644 ± 71†	692 ± 78 *	751 ± 85 *
Eadi					
$EAdi_{peak}$ (µV)	12.6 ± 2.5	13.6 ± 2.2 †	11.2 ± 1.5	9.3 ± 1.3 *	8.6 ± 1.3 *
$EAdi_{peak}/EAdi_{tp}$ (µV.sec^{-1})	21.7 ± 4.6	23.4 ± 4.3 †	19.8 ± 3.5	16.2 ± 2.7	15.2 ± 3.1 *
∫EAdi /breath (µV.sec)	10.1 ± 1.7	11.0 ± 1.5 †	8.9 ± 0.8	7.7 ± 0.9	7.7 ± 1.1
Comfort					
ATICE score	14.7 ± 1.2	14.3 ± 1.4	14.8 ± 1.3	15.2 ± 1.4	15.2 ± 1.3

ATICE = Adaptation to the Intensive Care Environment comfort score; $EAdi_{peak}$ = peak diaphragmatic electrical activity; $EAdi_{tp}$ = time to peak EAdi; $EAdi_{peak}/EAdi_{tp}$ = mean inspiratory rate of rise of EAdi; ∫EAdi = area under the EAdi waveform per breath; $NAVA_{1,2,3,4}$ = neurally adjusted ventilatory assist with a gain of 1, 2, 3 and 4 $cmH_2O.\mu V^{-1}$ EAdi; PSV = pressure support ventilation; RR = respiratory rate; T_E = expiratory time; T_I = inspiratory time; T_T = total respiratory cycle time; T_I/T_T = inspiratory duty cycle; V'_E = minute ventilation; V_T = tidal volume; V_T/kg, tidal per kg ideal body weight; V_T/T_I = mean inspiratory flow.

Data provided as mean values ± standard error of the mean.

* $p < 0.05$ *versus* PSV. † $p < 0.05$ *versus* $NAVA_4$

Table 2. Breathing Pattern Variability and autocorrelation Analysis during Pressure Support Ventilation and at Various Levels of NAVA

	PSV	$NAVA_1$	$NAVA_2$	$NAVA_3$	$NAVA_4$
Coefficient of variation					
V_T	11.1 ± 1.9	19.6 ± 2.9 †	24.0 ± 4.4 *	25.5 ± 2.6 *	31.1 ± 6.5 *
RR	10.4 ± 1.6	12.7 ± 1.8 †	15.5 ± 3.6	15.3 ± 2.4	19.6 ± 3.4 *
V'_E	10.8 ± 1.6	17 ± 2.0 †	20.2 ± 2.5 *†	22.1 ± 1.9 *	28.0 ± 4.5 *
T_I	9.6 ± 1.6	12.5 ± 1.7 †	15.8 ± 3.2 *†	16.5 ± 2.1 *†	22.7 ± 4.4 *
T_E	15.5 ± 2.6	16.0 ± 2.0 †	18.0 ± 2.7	20.4 ± 3.4	25.4 ± 5.0 *
T_T	11.4 ± 1.9	12.3 ± 1.5 †	14.5 ± 2.6	15.9 ± 2.4	19.8 ± 3.8 *
T_I/T_T	9.2 ± 1.6	11.6 ± 1.3 †	12.5 ± 1.5 †	14.5 ± 2.0 *	18.1 ± 2.3 *
V_T/T_I	6.6 ± 1.1	13.3 ± 1.8 *†	17.0 ± 2.3 *†	17.6 ± 1.3 *†	24.7 ± 3.7 *
Lag (number of cycles)					
V_T	8.1 ± 2.2	4.1 ± 2.3	3.9 ± 0.9	3.5 ± 0.5	3.7 ± 0.6
RR	12.1 ± 2.5	8.7 ± 3.0	8.9 ± 2.0	7.4 ± 1.8	4.4 ± 1.0
V'_E	3.8 ± 1.3	5.6 ± 1.5	5.1 ± 0.6	4.6 ± 1.0	4.1 ± 0.7
T_I	6.5 ± 1.4	2.9 ± 0.5	4.2 ± 0.7	3.8 ± 1.1	3.2 ± 0.7
T_E	9.2 ± 2.4	5.4 ± 1.7	6.5 ± 1.6	5.6 ± 1.2	3.7 ± 0.6
T_T	12.1 ± 2.6	7.4 ± 2.0	8.2 ± 1.9	6.3 ± 1.5	4.5 ± 1.1 *
T_I/T_T	2.2 ± 0.2	2.4 ± 0.2	3.1 ± 0.7	3.7 ± 1.4	2.4 ± 0.2
V_T/T_I	16.9 ± 3.9	7.4 ± 2.0 *	5.3 ± 0.6 *	4.8 ± 0.7 *	4.5 ± 0.7 *

Autocorrelation coefficient					
V_T	0.28 ± 0.05	0.18 ± 0.04	0.22 ± 0.04	0.16 ± 0.04	0.19 ± 0.04
RR	0.43 ± 0.04	0.20 ± 0.04 †	0.30 ± 0.04 †	0.24 ± 0.05 †	0.21 ± 0.03 *
V'_E	0.16 ± 0.06	0.18 ± 0.04	0.23 ± 0.04	0.18 ± 0.04	0.22 ± 0.04
T_I	0.25 ± 0.04	0.15 ± 0.04	0.18 ± 0.04	0.11 ± 0.02	0.14 ± 0.04
T_E	0.26 ± 0.04	0.17 ± 0.04	0.20 ± 0.04	0.19 ± 0.04	0.17 ± 0.04
T_T	0.38 ± 0.05	0.20 ± 0.04 *	0.27 ± 0.04	0.21 ± 0.04 *	0.18 ± 0.03 *
T_I/T_T	0.10 ± 0.03	0.17 ± 0.02	0.16 ± 0.03	0.16 ± 0.04	0.14 ± 0.04
V_T/T_I	0.45 ± 0.05	0.24 ± 0.05 *	0.28 ± 0.05 *	0.24 ± 0.04 *	0.19 ± 0.06 *

$NAVA_{1,2,3,4}$ = neurally adjusted ventilatory assist with a gain of 1, 2, 3, 4 $cmH_20/\mu V$ EAdi; PSV = pressure support ventilation; RR = respiratory rate; T_E = expiratory time; T_I = inspiratory time; T_T = total respiratory cycle time; T_I/Ttot = inspiratory duty cycle; V'_E = minute ventilation; V_T = tidal volume; V_T/ T_I = mean inspiratory flow.

Data provided as mean values ± standard error of the mean.

* $p < 0.05$ *versus* PSV, † $p < 0.05$ *versus* $NAVA_4$.

Table 3. Breath-to-breath Variability and Autocorrelation Analysis of Diaphragm Electrical Activity (EAdi) during Pressure Support Ventilation and at Various Levels of NAVA.

	PSV	**$NAVA_1$**	**$NAVA_2$**	**$NAVA_3$**	**$NAVA_4$**
Coefficient of variation (%)					
$EAdi_{peak}$	28.9 ± 2.6	23.6 ± 1.8 †	27.7 ± 2.5	28.4 ± 1.9	33.0 ± 3.5
$EAdi_{peak}/EAdi_{tp}$	35.3 ± 3.1	31.6 ± 3.2 †	34.7 ± 3.0 †	35.6 ± 2.7 †	44.6 ± 4.8 *
∫EAdi	28.9 ± 8.7	23.6 ± 6.1	27.7 ± 8.2	28.4 ± 6.3	33.0 ± 11.8
Lag (number of cycles)					
$EAdi_{peak}$	16.4 ± 5.5	5.6 ± 0.9	6.5 ± 0.9	7.4 ± 1.3	7.6 ± 2.7
$EAdi_{peak}/EAdi_{tp}$	2.4 ± 0.2	2.9 ± 0.2	2.5 ± 0.2	2.6 ± 0.2	2.6 ± 0.9
∫EAdi	11.6 ± 4.1	9.4 ± 4.3	5.2 ± 0.9	7.3 ± 1.8	7.7 ± 2.0
Autocorrelation coefficient					
$EAdi_{peak}$	0.38 ± 0.06	0.24 ± 0.05	0.33 ± 0.04	0.28 ± 0.05	0.32 ± 0.04
$EAdi_{peak}/EAdi_{tp}$	0.15 ± 0.04	0.21 ± 0.04	0.17 ± 0.03	0.15 ± 0.04	0.16 ± 0.04
∫EAdi	0.29 ± 0.05	0.22 ± 0.04	0.27 ± 0.04	0.23 ± 0.05	0.26 ± 0.05

$EAdi_{peak}$ = peak EAdi; $EAdi_{tp}$ = time to peak EAdi; $EAdi_{peak}/EAdi_{tp}$ = rate of rise of EAdi; ∫EAdi = area under the EAdi waveform per breath; NAVA1,2,3,4 = neurally adjusted ventilatory assist with a gain of 1, 2, 3, 4 $cmH_2O.\mu V^{-1}$ diaphragmatic electrical activity (EAdi); PSV = pressure support ventilation;

Data provided as means ± standard error of the mean.

* $p < 0.05$ *versus* PSV, † $p < 0.05$ *versus* $NAVA_4$

Table 4. Complexity of Ventilatory Flow and Diaphragmatic Electrical Activity (EAdi).

	PSV	**$NAVA_1$**	**$NAVA_2$**	**$NAVA_3$**	**$NAVA_4$**
Flow					
Noise limit	>0	>0	>0	>0	>0
LLE (bits/iteration)	0.50 ± 0.05	0.55 ± 0.04	0.63 ± 0.02 *	0.63 ± 0.03 *	0.65 ± 0.03 *
KSE (bits/iteration)	0.50 ± 0.06	0.56 ± 0.05	0.66 ± 0.04 *	0.65 ± 0.04 *	0.68 ± 0.04 *
EAdi					
Noise limit	>0	>0	>0	>0	>0
LLE (bits/iteration)	0.57 ± 0.04	0.55 ± 0.04	0.56 ± 0.03	0.56 ± 0.04	0.55 ± 0.03
KSE (bits/iteration)	0.68 ± 0.05	0.64 ± 0.06	0.65 ± 0.04	0.67 ± 0.05	0.67 ± 0.05

EAdi = diaphragmatic electrical activity; KSE = Kolmogorov- Sinai entropy; LLE = largest Lyapunov exponent; $NAVA_{1,2,3,4}$, = neurally adjusted ventilatory assist with a gain of 1, 2, 3, 4 $cmH_20/\mu V$ EAdi; PSV = pressure support ventilation.

Data provided as means ± standard error of the mean.

* $p < 0.05$ *versus* PSV

Table 5. Correlation between the Coefficient of Variation of Breathing Pattern or Electrical Activity of the Diaphragm (EAdi) Indices with the Largest Lyapunov Exponents of the Flow (LLE_{flow}) and EAdi (LLE_{EAdi}).

	R (IC95%)	***p* value**
Correlation with LLE_{flow}		
CV-V_T	0.32 (0.07 to 0.54)	0.01
CV-RR †	0.30 (0.04 to 0.52)	0.02
CV-T_I/T_T	0.40 (0.16 to 0.60)	0.002
CV-V_T/T_I	0.38 (0.14 to 0.58)	0.003
Correlation with LLE_{EAdi}		
CV-$EAdi_{peak}$	-0.14 (-0.39 to 0.13)	NS
CV-∫Eadi †	0.07 (-0.21 to 0.33)	NS
CV-$EAdi_{peak}/EAdi_{tp}$	-0,16 (-0,40 to 0.11)	NS

CV = coefficient of variation; CV-$EAdi_{peak}$ = CV of the maximum diaphragmatic electrical activity; CV-∫Eadi = CV of the area under the EAdi waveform per breath; CV-RR = CV of the respiratory rate; CV-T_I/T_T = CV of the flow-based inspiratory duty cycle; CV-V_T = CV of the tidal volume; CV-V_T/T_I = CV of the mean inspiratory flow; CV-$EAdi_{peak}/EAdi_{tp}$ = CV of the EAdi rising slope; EAditp = time to peak of EAdi; IC95% = 95% confidence interval; R = Pearson correlation;

† = nonparametric test (Spearman correlation)

Chapitre 2

L'utilisation du mode NAVA en ventilation non invasive (VNI) permet d'améliorer la synchronisation patient-ventilateur en post extubation.

Nous avons montré dans le chapitre 1 que le mode NAVA améliorait les interactions patient-ventilateur. En VNI, assurer une interaction optimale entre le patient et son ventilateur est un enjeu quotidien. En effet, les fuites autour du masque contribuent largement à la genèse d'asynchronies patient ventilateur (141). Ceci est d'autant plus fréquent en post-extubation quand la sonde gastrique est parfois laissée en place pour la nutrition ou l'administration de certains médicaments. Dans le contexte du post-extubation, la VNI est bénéfique puisqu'elle prévient la ré-intubation chez les patients à risque de détresse respiratoire aiguë (142-144). Toutefois, en générant des asynchronies patient ventilateur, les fuites autour du masque peuvent compromettre cet effet protecteur (145). Pour compenser ces fuites, fréquentes en VNI, la plupart des ventilateurs de dernière génération sont équipés d'un algorithme dédié à la VNI. Ces algorithmes améliorent les interactions patient-ventilateur, mais cette amélioration n'est que partielle.

Asservir le déclenchement et le cyclage du ventilateur à un signal EMG en lieu et place du débit et de la pression aux voies aériennes pourrait permettre de s'affranchir des conséquences délétères liées aux fuites. Le NAVA pourrait donc diminuer la prévalence des asynchronies patient-ventilateur induite par les fuites. Dix sept patients recevant une VNI prophylactique en post-extubation ont été étudiés. Chaque patient était ventilé lors de 4

périodes randomisées de 10 minutes : VSAI sans algorithme VNI (PSV-NIV-), VSAI avec algorithme VNI (PSV-NIV+), NAVA sans algorithme VNI (NAVA-NIV-) et, NAVA avec algorithme VNI (NAVA-NIV+). Initialement, le niveau d'aide inspiratoire en VSAI était réglé pour obtenir un volume courant de 6 à 8mL/kg puis, lors du passage en mode NAVA, le niveau de NAVA était choisi pour obtenir une pression de pic similaire à celle obtenu en VSAI.

Au cours de ces 4 périodes, les descripteurs du profil ventilatoire, l'EAdi, la proportion de fuite, le délai de trigger inspiratoire, le temps inspiratoire en excès, le nombre de cycles longs, le nombre de cycles courts, les appels inefficaces, les doubles déclenchements et les autodéclenchements ont été quantifiés. Les principales asynchronies ont été quantifiées et deux index d'asynchronies ont été calculés : l'un global et l'autre lié aux fuites.

La pression de pic et l'EAdi étaient similaires en VSAI et en NAVA, témoignant d'un même niveau d'assistance dans les 4 conditions. L'algorithme VNI réduisait la proportion de fuites en VSAI et en NAVA mais n'avait pas d'impact majeur sur le délai de trigger inspiratoire et sur l'index global d'asynchronies. En revanche, le temps inspiratoire en excès, l'index d'asynchronie global et l'index lié aux fuites étaient significativement inférieurs en mode NAVA. Toutefois, un plus grand nombre de doubles déclenchements était détecté dans le mode NAVA. Il n'existait pas d'impact du NAVA en VNI sur la dyspnée ou le confort.

En conclusion, cette première étude sur la VNI en mode NAVA a permis de montrer que la combinaison du mode NAVA avec l'algorithme VNI offrait le meilleur compromis entre une bonne synchronisation patient-ventilateur et un faible niveau de fuite.

Les données issues de ce deuxième travail ont fait l'objet d'une publication scientifique dans *Critical Care Medicine* (146).

Neurally adjusted ventilatory assist improves patient–ventilator interaction during postextubation prophylactic noninvasive ventilation*

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Objectives: **To compare the respective impact of pressure support ventilation and naturally adjusted ventilatory assist, with and without a noninvasive mechanical ventilation algorithm, on patient–ventilator interaction.**

Design: **Prospective 2-month study.**

Setting: **Adult critical care unit in a tertiary university hospital.**

Patients: **Seventeen patients receiving a prophylactic postextubation noninvasive mechanical ventilation.**

Interventions: **Patients were randomly mechanically ventilated for 10 mins with: pressure support ventilation without a noninvasive mechanical ventilation algorithm (PSV-NIV–), pressure support ventilation with a noninvasive mechanical ventilation algorithm (PSV-NIV+), neurally adjusted ventilatory assist without a noninvasive mechanical ventilation algorithm (NAVA-NIV–), and neurally adjusted ventilatory assist with a noninvasive mechanical ventilation algorithm (NAVA-NIV+).**

Measurements and Main Results: **Breathing pattern descriptors, diaphragm electrical activity, leak volume, inspiratory trigger delay, inspiratory time in excess, and the five main asynchronies were quantified. Asynchrony index and asynchrony index influenced by leaks were computed. Peak inspiratory pressure and diaphragm electrical activity were similar for each of the four experimental conditions. For both pressure support ventilation and neurally adjusted ventilatory assist, the noninvasive mechanical ventilation algorithm significantly reduced the level of leakage ($p < .01$). Inspiratory trigger delay was not affected by the noninvasive mechanical ventilation algorithm but was shorter in neurally adjusted ventilatory assist than in pressure support ventilation ($p < .01$). Inspiratory time in excess was shorter in neurally adjusted ventilatory assist and PSV-NIV+ than in PSV-NIV– ($p < .05$). Asynchrony index was not affected by the noninvasive mechanical ventilation algorithm but was significantly lower in neurally adjusted ventilatory assist than in pressure support ventilation ($p < .05$). Asynchrony index influenced by leaks was insignificant with neurally adjusted ventilatory assist and significantly lower than in pressure support ventilation ($p < .05$). There was more double triggering with neurally adjusted ventilatory assist.**

Conclusions: **Both neurally adjusted ventilatory assist and a noninvasive mechanical ventilation algorithm improve patient–ventilator synchrony in different manners. NAVA-NIV+ offers the best compromise between a good patient–ventilator synchrony and a low level of leaks. Clinical studies are required to assess the potential clinical benefit of neurally adjusted ventilatory assist in patients receiving noninvasive mechanical ventilation.**

Trial Registration: **Clinicaltrials.gov Identifier NCT01280760. (Crit Care Med 2012; 40:1738–1744)**

Key Words: mechanical ventilation; neurally adjusted ventilator assist; noninvasive ventilation; patient–ventilator interaction; positive pressure support

Postextubation prophylactic noninvasive ventilation (NIV) prevents reintubation in selected "at-risk" intensive care unit populations (1–3). The efficacy of NIV can be compromised by leaks at the patient–mask interface (4) that promote patient–ventilator asynchronies (5). In the postextubation setting, leaks can become a major issue if the nasogastric feeding tube is left in place for the purpose of enteral feeding and drug administration. Ventilator manufacturers have developed NIV algorithms to take leaks into account (6) with positive effects on patient–ventilator synchrony (7).

Subordinating the ventilator cycle to an electromyographic respiratory signal instead of flow or airway pressure, as during neurally adjusted ventilatory assist (NAVA), should radically alleviate the impact of leaks on patient–ventilator synchrony. It is of note that NAVA improves patient–ventilator interaction in intubated patients in whom leaks are not an issue (8–11).

In the present study, we hypothesized that NAVA would efficiently reduce leak-related patient–ventilator asynchronies during postextubation prophylactic NIV. We therefore set out to compare pressure support ventilation (PSV), PSV with a specific NIV algorithm, and NAVA in

***See also p. 1968.**

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terms of patient–ventilator synchrony. We also sought to evaluate the putative benefit of a recently introduced specific NAVA-NIV algorithm on patient–ventilator interaction.

PATIENTS AND METHODS

The study was conducted over a 2-month period (January 1, 2011, to March 1, 2011) in a ten-bed intensive care unit within an 1800-bed university hospital. The protocol was approved by the institutional review board of the French Learned Society for Respiratory Medicine (Société de Pneumologie de Langue Française). Informed consent was obtained from the patients.

Patients. Patients initially intubated and ventilated in the intensive care unit were eligible for inclusion in the study if: 1) they had been extubated for <2 hrs; 2) they had previously been mechanically ventilated with NAVA mode and the NAVA catheter had been left in place; 3) a prophylactic postextubation NIV had been decided; 4) sedations had been stopped >12 hrs previously; and 5) postextubation Glasgow scale ≥14. The final decision to institute NAVA depended on the physician in charge of the patient who was not involved in the research. However, preconditions for the institution of NAVA included 1) poor clinical tolerance of PSV for at least 2 hrs when adjusted to provide a tidal volume of 6–8 mL/kg at a setting not exceeding 20 cm H_2O; this was decided by the clinician in charge of the patient, either as a result of a direct indication by the patient that his or her breathing was a matter of discomfort or according to usual clinical criteria (12–14); 2) a Ramsay sedation scale score <4; 3) F_{IO_2} ≤50% and positive end-expiratory pressure ≤10 cm H_20; 4) hemodynamic stability without vasopressor or inotropic medication; and 5) estimated remaining duration of mechanical ventilation >48 hrs. The exclusion criteria for using the NAVA mode in invasive ventilation were mainly related to contraindications to the use of NAVA: known or suspected phrenic nerve dysfunction, impaired respiratory drive, neuromuscular disease, and contraindications to electrical activity of the diaphragm (EAdi) catheter placement (e.g., esophageal varices or obstruction, recent gastroesophageal surgery, facial surgery or trauma, or upper gastrointestinal bleeding).

Based on the results of previously published studies, a prophylactic postextubation NIV is instituted in our unit if one of the following criteria is present: 1) age >65 yrs; 2) at least two consecutive failures of weaning trials; 3) chronic heart failure as the cause of mechanical ventilation; 4) Pa_{CO_2} ≥45 mm Hg after extubation; 5) weak cough; and 6) chronic respiratory disorders with hypercapnia during a spontaneous breathing through T-piece trial (1, 2, 15). Criteria for exclusion from the study were the classic contraindications to NIV: recent gastric or esophageal surgery, active upper gastrointestinal bleeding, facial or cranial trauma or surgery, anatomical abnormalities interfering with the fit of the mask, an excessive amount of respiratory secretions, inability to protect the airways, problems with swallowing, and uncontrolled cardiac ischemia or arrhythmias (16). Patients unable to cooperate during NIV and patients with do-not-intubate orders were not included in the study.

Ventilator. All patients were ventilated using a Servo-i (Maquet Critical Care, Solna, Sweden) ventilator equipped with the standard commercial version of the NAVA module. All ventilators were also equipped with the standard commercial version of the NIV algorithms for PSV and NAVA. The NIV algorithm, so-called "NIV mode," measures and compensates leaks to minimize their deleterious impact on patient–ventilator synchrony. To achieve this goal, flow and triggers are automatically adjusted. Bedside studies have demonstrated the benefit of NIV algorithms on patient–ventilator synchrony (5, 6).

Study Protocol. One hr after extubation, the position of the EAdi NAVA catheter (16 Fr) was controlled according to the manufacturer's recommendations (17). NIV was applied with an oronasal mask (Performatrak, Respironics, Murrysville, PA). The leaks were minimized by means of an adjustable harness.

The ventilator was initially set in pressure support mode with the NIV algorithm. Positive end expiratory pressure was set at 4 cm H_2O. Inspiratory pressure support level was adjusted to target a tidal volume of 6–8 mL/kg. Inspiratory slope was 100 msec and expiratory trigger was 30% (default value). The fractional concentration of oxygen was set to achieve a SpO_2 of 92% to 96%. The ventilator was then switched to NAVA. The NAVA level was set in such a way as to produce the same peak pressure as during PSV. Thereafter, patients were ventilated for 10 mins under each of the following four conditions in random order: pressure support without the noninvasive ventilation algorithm (PSV-NIV–), pressure support with the noninvasive ventilation algorithm (PSV-NIV+), NAVA without the noninvasive ventilation algorithm (NAVA-NIV–), and NAVA with the noninvasive ventilation algorithm (NAVA-NIV+). The positioning of the mask was kept unchanged during the four study periods.

Data Acquisition. Airway pressure, flow, and EAdi were acquired at 100 Hz from the ventilator through a RS232 interface connected to a computer using commercially available software (Servo-i RCR, version 3.6.2; Maquet Critical Care). At the end of each study period, dyspnea was graded by means of a visual analog scale, and respiratory comfort was evaluated using Campbell's respiratory distress observation scale (18).

Data Analysis. All the respiratory cycles under NAVA conditions were included in the analysis, including those that were pneumatically triggered.

Measurements and Time Parameters. The following descriptors of the breathing pattern were measured: ventilator respiratory rate determined by airway pressure and flow recordings, neural respiratory rate determined by EAdi recordings, inspired tidal volume, expired tidal volume, minute ventilation, peak airway pressure, ventilator pressurization time defined as the time difference between the beginning and the end of inspiratory flow, neural inspiratory time defined as the time difference between the beginning of the increase in the EAdi signal and its maximal value, and maximum electrical activity of the diaphragm. Leaks were calculated as (inspired tidal volume – expired tidal volume)/inspired tidal volume. The inspiratory trigger delay (Td_{insp}) was calculated as the time difference between the beginning of the increase in the EAdi signal and the beginning of the ventilator inspiratory flow. In the same manner, the inspiratory time in excess (Ti_{excess}) of neural inspiratory time was defined as [(ventilator pressurization time – neural inspiratory time)/neural inspiratory time] × 100 (8, 19, 20).

Patient–Ventilator Asynchrony. The five main types of asynchronies were quantified accordingly to previously published definitions (7, 9, 13) and are described in Table 1: 1) ineffective efforts; 2) autotriggering; 3) premature cycling; 4) delayed cycling; and 5) double triggering, which was separated into two groups. Type I double triggering is the consequence of a biphasic EAdi signal, whereas type II double triggering is when a one neural inspiration triggers two pneumatic cycles. The number of each type of asynchrony was reported as the total number of each event per minute. A global asynchrony index (AI) was computed as previously published (13, 21). An AI >10% was considered severe (13, 21). In addition, because leak-related asynchronies are a major cause of patient–ventilator asynchrony in NIV, we also calculated the AI specific to leaks (AI_{leaks}) that only integrates leak-related asynchronies, namely ineffective efforts, autotriggering, and late cycling (5).

Statistical Analysis. The statistical analysis was performed with Prism 4.01 software (GraphPad Software, San Diego, CA). Normality testing failed for all results (Kolmogorov-Smirnov). Results are therefore reported as median (25–75 interquartile range). A Friedman test was performed to compare the four conditions followed, when indicated, by a pairwise comparison using Dunn's *post hoc* test. The relationship between leaks and Ti_{excess} of each condition was examined with Spearman's correlation. Global effect of NAVA vs. PSV and effect of the NIV algorithm were analyzed on four main descriptors of patient–ventilator interaction: Td_{insp}, Ti_{excess}, AI, and AI_{leaks}. Thus, four linear mixed effect models

Table 1. Definition of asynchronies

Asynchronies	Definitions
Ineffective effort, n.min^{-1}	Presence of a characteristic EAdi activity not followed by a ventilator-delivered pressurization
Late cycling, n.min^{-1}	Duration of pressurization at least twice as long as the patient's neural inspiratory time
Double triggering type I, n.min^{-1}	Aspect of two pneumatic cycles as a consequence of a biphasic EAdi signal
Double triggering type II, n.min^{-1}	One neural inspiration triggers two pneumatic cycles
Premature cycling, n.min^{-1}	Duration of pressurization at least twice as long as the patient's neural inspiratory time
Autotriggering, n.min^{-1}	A cycle delivered by the ventilator in the absence of EAdi signal
Asynchrony index, %	[(autotriggering + ineffective efforts + late cycling + premature cycling +double triggering)/(ineffective effort + pneumatic respiratory rate)] × 100
Asynchrony index specific to leaks, %	[(autotriggering + ineffective efforts + late cycling)/(ineffective effort + pneumatic respiratory rate)] × 100

EAdi, electrical activity of the diaphragm.

The number of each type of asynchrony was reported as the total number of each event per minute (n.min^{-1}). Asynchrony index specific to leaks (%) takes into account only the asynchronies influenced by leaks (ineffective efforts, autotriggering, and late cycling), but not those that are not influences by leaks (double-triggering and premature cycling) (7).

with random intercept, which account for repeated measures in the same patient, were used to assess the effect of NAVA and NIV on four outcomes. When necessary, an interaction term between ventilation mode (NAVA or PSV) and NIV algorithm was added to the model. Results are reported as the mean estimated effect together with its 95% confidence interval (95% CI). Statistical analysis of the global effect was performed using the Open Source R software (>R 2.10.1, R Development Core Team 2009; R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided and $p < .05$ was considered to indicate significance.

RESULTS

The study pertains to a convenience sample of 17 patients. Their main characteristics and the reasons why a postextubation prophylactic NIV was instituted are summarized in Table 2. Sedation had been discontinued at least 12 hrs before a spontaneous breathing trial, and Glasgow Coma Score at the time of extubation was ≥14 in all patients. All the patients were retained for the analysis. Ventilator settings and representative breathing pattern variables are summarized in Table 3.

It was possible to successfully achieve NAVA in all the patients. Automatic reversion to PSV was never observed during the two 10-min periods under NAVA. During NAVA, EAdi was used to trigger 94% (84% to 96%) of the breaths in NAVA-NIV– and 85% (80% to 90%) in NAVA-NIV+. The level of ventilatory assistance, as assessed by peak airway pressure was similar in the four conditions (Table 3).

Table 2. Main patient characteristics at enrolment and outcome parameters

Age, yrs	64 (58–77)
Male, no. (%)	7 (41)
Body mass index, kg/m^2	26 (21–35)
Simplified Acute Physiologic Score II	49 (41–59)
Reasons for invasive mechanical ventilation, no. (%)	
Acute on chronic respiratory failure	4 (23)
Community-acquired pneumonia	4 (23)
Cardiogenic pulmonary edema	2 (12)
Septic shock	3 (18)
Coma	3 (18)
Postoperative acute respiratory failure	1 (6)
Reasons for postextubation prophylactic noninvasive ventilation, no. (%)[a]	
Age >65 yrs	8 (47)
Failure of weaning trial >1	5 (29)
Chronic heart failure	4 (23)
Chronic respiratory disorders	4 (23)
$PaCO_2$ ≥45 mm Hg after extubation	10 (59)
Weak cough	2 (12)
Duration of invasive mechanical ventilation, days	3 (6-2)
Intensive care unit length of stay, days	6 (3-10)
Intensive care unit mortality, no. (%)	3 (18)

Data are expressed as median (25–75 interquartile range) except otherwise stated.

[a]A given patient may have more than one reason for postextubation prophylactic noninvasive ventilation.

Breathing Pattern. The NIV algorithm was efficient at reducing leaks (less leaks with PSV-NIV+ and NAVA-NIV+ than with PSV-NIV– and NAVA-NIV–; Fig. 1), whereas switching from PSV to NAVA had no impact on leaks. Neural and ventilator respiratory rates were similar among the four conditions as was neural inspiratory time. Expiratory tidal volume was significantly higher in PS-NIV+ than in other conditions (Fig. 1). Maximum EAdi was similar in the four conditions (Fig. 1).

Inspiratory and Expiratory Trigger Delay. In both PSV and NAVA, Td_{insp} was not influenced by NIV algorithms but was significantly shorter in NAVA than in pressure support (PSV-NIV– vs. NAVA-NIV– and PSV-NIV+ vs. NAVA-NIV+; Fig. 2).

On the contrary, the NIV algorithm significantly shortened Ti_{excess} in PSV, but NAVA did not further reduce Ti_{excess} compared with PSV (Fig. 2). Ti_{excess} was correlated with leaks in PSV-NIV– ($r = 0.82, p < .00001$), whereas no correlation with leaks was found in PSV-NIV+ and NAVA.

In terms of global effect, NAVA significantly decreased Td_{insp} (–198; 95% CI, –63; –132 ms; $p < .001$), whereas NIV algorithm had no significant effect (–32; 95% CI –97; –34 ms; $p = .34$). Regarding Ti_{excess}, there was an interaction between the effect of NAVA and of the NIV algorithm. Indeed, NAVA reduced significantly Ti_{excess} without the NIV algorithm (–270; 95% CI –450; 100 ms; $p < .001$) but not with the NIV algorithm (–40; 95% CI –90; –10 ms; $p = .11$), whereas the NIV algorithm reduced significantly Ti_{excess} with PSV (–260; 95% CI –440; –80; $p < .001$) but not with NAVA (–30; 95% CI –70; 10 ms; $p = .18$).

Patient–Ventilator Asynchrony. Table 4 depicts the respective prevalence of the main asynchronies. In the four conditions, both ineffective efforts and autotriggering were infrequent if not absent. The prevalence of double triggering was significantly lower in PSV-NIV+ than in NAVA-NIV+. Type I double triggering was only observed in NAVA, whereas the prevalence of type 2 double triggering was similar among the four conditions. As compared with PSV, NAVA significantly reduced the prevalence of late cycling, whereas NIV algorithms had no influence on this type of asynchrony. Finally, NAVA reduced the prevalence of premature cycling, but the difference

Table 3. Ventilator settings and representative breathing pattern variables

	Study Period			
	PSV-NIV–	PSV-NIV+	NAVA-NIV–	NAVA-NIV+
Pressure support level, cm H_2O	10 (9–10)	10 (9–10)	—	—
NAVA gain level, cm $H_2O\mu V^{-1}$	—	—	0.7 (0.5–1.0)	0.7 (0.5–1.0)
Peak airway pressure, cm H_2O	15.2 (14.3–15.9)	14.9 (13.8–15.1)	15.4 (14.5–18.5)	15.1 (12.7–16.1)
Ventilator respiratory rate, n/min	24.0 (22.0–29.0)	23.0 (20.5–30.0)	24.0 (22.5–29.0)	24.0 (22.0–29.5)
Neural respiratory rate, n/min	24.0 (21.0–28.5)	23.0 (22.0–30.5)	24.0 (21.0–27.0)	24.0 (22.0–27.0)
Expired tidal volume				
mL	303 (246–400)	424 (343–471)[a]	263 (190–387)[b]	324 (280–380)[b]
$mL.kg^{-1}$	4.8 (4.1–6.2)	6.9 (5.7–7.5)[a]	4.8 (3.2–6.2)[b]	5.8 (4.2–6.4)[b]
Leaks				
(%)	56 (45–70)	13 (9–23)[a]	61 (44–67)[b]	26 (17–33)[ac]
Minute ventilation, $L.min^{-1}$	18.5 (14.7–25.0)	12.0 (9.0–13.7)[a]	15.4 (13.2–22.2)[b]	12.3 (10.1–14.2)[ac]
Inspiratory trigger delay, ms	225 (165–370)	203 (129–265)	51 (18–107)[ab]	57 (19–81)[ab]
Ventilator pressurization time, ms	1060 (695–1380)	860 (720–960)[a]	920 (705–1030)	870 (700–1030)[a]
Neural inspiratory time, ms	780 (625–915)	750 (605–930)	860 (615–915)	790 (610–930)
Duration of pressurization by the ventilator in excess of neural inspiratory time				
ms	320 (115–665)	140 (80–180)[a]	130 (60–160)[a]	100 (45–150)[a]
Percent of neural inspiratory time	38.5 (22.4–83.2)	17.5 (10.2–21.7)[a]	14.9 (9.7–20.6)[a]	12.3 (8.0–17.3)[a]
Maximum electrical activity of the diaphragm, μV	11.6 (8.5–18.9)	13.9 (7.4–20.9)	12.7 (10.3–19.2)	11.6 (9.5–15.6)

PSV-NIV+ and PSV-NIV–, pressure support ventilation with and without noninvasive ventilation algorithm, respectively; NAVA-NIV+ and NAVA-NIV–, neurally adjusted ventilatory assist with and without noninvasive ventilation algorithm.

was only significant between PSV-NIV+ and both NAVA-NIV+ and NAVA-NIV–. However, because the ventilator is triggered and cycled off by the EAdi in NAVA, no premature cycling was to be expected. It appears that the little premature cycling observed in NAVA was always observed during pneumatically triggered cycles.

Overall, the asynchrony index was significantly lower in NAVA-NIV– and NAVA-NIV+ than in PSV-NIV– and PSV-NIV+ (Fig. 3). In other words, NAVA was more efficient than the NIV algorithm in reducing overall patient–ventilator asynchrony. AI_{leaks} was close to zero with NAVA and significantly lower than with pressure support (Fig. 3). In PSV, there was a nonsignificant trend toward a lower AI_{leaks} when the NIV algorithm was activated. Switching to NAVA reduced the number of patients with severe AI (16 [95%] and 17 [100%], respectively, in PSV-NIV+ and PSV-NIV– vs. ten [59%] and eight [47%] in NAVA-NIV+ and NAVA-NIV–). No severe AI_{leaks} were observed in NAVA, whereas five (29%) and ten (59%) patients had severe AI_{leaks} in PSV-NIV+ and PSV-NIV–, respectively.

In terms of global effect, there was an interaction between the effect of NAVA and of the NIV algorithm on both AI and AI_{leaks}. Indeed, NAVA significantly diminished both AI and AI_{leaks} with the NIV algorithm (–16.1; 95% CI –23.1%; –9.1%; $p <$ .001 and –5.6; 95% CI –8.4%; –2.8%; $p <$ .001, respectively) and without the NIV algorithm (–30.5; 95% CI –41.2%; –19.7%; $p <$ .001 and –16.9; 95% CI –25.0%; –8.8%; $p <$ .001 respectively). The NIV algorithm reduced both AI and AI_{leaks} with PSV (–12.2; 95% CI –24.1%; –0.3%; $p <$ .001 and –11.1; 95% CI –19.6%; –2.7%; $p <$ .001, respectively), but not with NAVA (2.1; 95% CI –1.4%; 5.7%; $p = .22$ and 0.1; 95% CI –0.3%; 0.6%; $p = .54$, respectively).

Comfort and Dyspnea. The mode (PSV and NAVA) and the presence or absence of an NIV algorithm had no influence on dyspnea-visual analog scale, which was similar among the four conditions (1 [0–2] in PSV-NIV–, 1 [0–3] in PSV-NIV+, 2 [0–3] in NAVA-NIV–, and 1 [0–2] in NAVA-NIV+). Similarly, no significant change in the respiratory distress observation scale score was detected (1 [0–1] in PSV-NIV–, 0 [0–1] in PSV-NIV+, 1 [0–1] in NAVA-NIV–, and 1 [0–1] in NAVA-NIV+).

DISCUSSION

In this study, NAVA improved patient–ventilator interaction more than the activation of a specific NIV algorithm during PSV. The combination of NAVA with a specific NIV algorithm seemed to offer the best compromise between a good patient–ventilator synchrony and a low level of leaks. In addition, the study suggests that NAVA can be reliably and safely delivered to patients receiving NIV.

Trigger and Cycling Delay. Without the NIV algorithm, the average delay for triggering in PSV was high and way over the 150 msec beyond which a healthy subject is likely to perceive the inspiratory effort (22). This constitutes a potential source of dyspnea that was however not found in this study. The NIV algorithm did not significantly reduce the Td_{insp}, thus confirming in humans what had been suggested by a previous bench study: some NIV algorithms fail to counterbalance the deleterious effect of leaks on Td_{insp} (6). Conversely, NAVA did significantly reduce the Td_{insp}, which is not surprising because NAVA is not governed by respiratory pressure and flow, but rather by electromyographic activity of the diaphragm. This positive impact of NAVA on Td_{insp} had been previously observed in intubated patients (8, 9, 19, 20). The present observations reinforce the notion that this beneficial effect of NAVA can be observed despite a high level of leaks. Dyspnea-visual analog scale and the respiratory distress observation scale score were very low in the four experimental conditions. This probably explains why they were not influenced by NIV algorithms or NAVA despite the fact that the latter reduced Td significantly below 150 msec. With NIV, late cycling, a consequence of an exten-sion of ventilator insufflation into neural expiration (19, 23, 24), is another deleterious consequence of leaks (7, 25, 26). NIV algorithms have

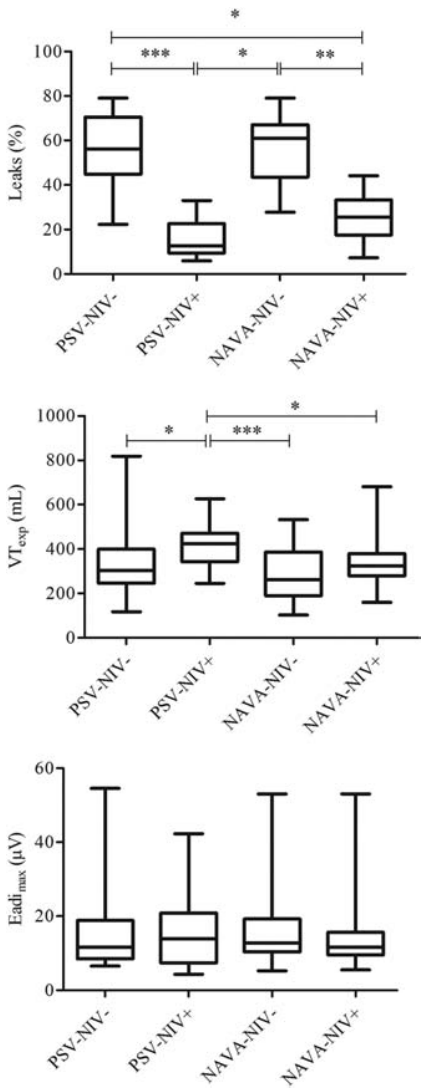

Figure 1. Effects of ventilator mode and non invasive ventilation algorithm on leaks, expiratory tidal volume, and maximal electrical activity of the diaphragm. Data are whiskers: minimum to maximum. $*p < .05$; $**p < .01$; $***p < .001$. VT_{exp}, Expiratory tidal volume; $EAdi_{max}$, maximal electrical activity of the diaphragm; *PSV-NIV+*, pressure support ventilation with noninvasive ventilation algorithm; *PSV-NIV−*, pressure support ventilation without noninvasive ventilation algorithm; *NAVA-NIV+*, neurally adjusted ventilatory assist with noninvasive ventilation algorithm; *NAV-NIV−*, neurally adjusted ventilatory assist without noninvasive ventilation algorithm.

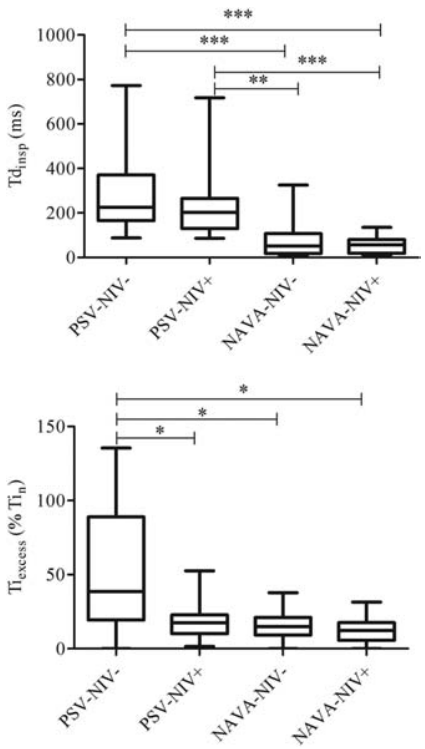

Figure 2. Effects of ventilator mode and noninvasive ventilation algorithm on inspiratory trigger delay and inspiratory time in excess. Ti_{excess} is defined as $[(Ti_v - Ti_n)/Ti_n] \times 100$, where Ti_v is the ventilator pressurization time and Ti_n is the neural inspiratory time. Data are whiskers: minimum to maximum. $*p < .05$; $**p < .01$; $***p < .001$. Td_{insp}, Inspiratory trigger delay; Ti_{excess}, inspiratory time in excess, *PSV-NIV+*, pressure support ventilation with noninvasive ventilation algorithm; *PSV-NIV–*, pressure support ventilation without noninvasive ventilation algorithm; *NAVA-NIV+* neurally adjusted ventilatory assist with noninvasive ventilation algorithm; *NAVA-NIV−*, neurally adjusted ventilatory assist without noninvasive ventilation algorithm,

been shown to prevent delayed cycling (5), which our study confirms, by a reduction of Ti_{excess}. Interestingly, NAVA did not further reduce Ti_{excess}, whereas it logically should have done so because cycling off depends on the EAdi signal. However, NAVA did reduce significantly the prevalence of late cycling asynchrony. A possible explanation of this discrepancy is that, compared with PSV, NAVA reduced not only the prevalence of the late cycling asynchrony, but also the prevalence of premature cycling, an asynchrony that has been shown to be increased by the Servo-i NIV algorithm as a consequence of an overcorrection of Ti_{excess}. It therefore seems that the summation of both beneficial (premature and late cycling reduction) yet contradictory effects of NAVA on Ti_{excess} led to the absence of any significant change of Ti_{excess}.

Patient–Ventilator Asynchrony. As a consequence of a better patient–ventilator interaction, NAVA reduces the prevalence of asynchrony in intubated patients (9, 10). We observed a similar phenomenon in our NIV patients. However, NAVA-NIV+ did significantly increase double triggering as compared with PSV-NIV+. Two types of double triggering have been described in NAVA (9). Type I double triggering is the consequence of a biphasic EAdi signal and its significance is unknown, a reason why it cannot be considered as a patient–ventilator asynchrony strictly speaking. With type 2 double triggering, however, one neural inspiration triggers two pneumatic cycles, which does correspond to a real asynchrony. In our study, NAVA-NIV+ did significantly increase double triggering as compared with PSV-NIV+. The main explanation for this result is probably the higher incidence of type I double triggering with NAVA, a well-demonstrated phenomenon (9). Furthermore, in our study, type 1 double triggering was only observed in NAVA and accounted for the higher prevalence of double triggering in NAVA.

When we focused on leak-related asynchronies using the previously described AI_{leaks}, NAVA proved to be efficient in reducing asynchronies, whereas the NIV algorithm did not, which is different from what had previously been reported (5). However, it is important to note that among the three leak-related asynchronies computed in AI_{leaks}, late cycling was the main one to be observed, whereas, despite a high level of leaks, both autotriggering and ineffective efforts were very rare if not absent (13, 27, 28). Therefore, the beneficial impact of the NIV algorithm or NAVA on their reduction could not be assessed.

Study Limitations. First, the decision to institute NAVA depended on the physician in charge of the patient. Despite the fact that this physician was not involved in the research, it is a potential selection bias. Second, NIV was delivered for prophylactic reasons to prevent reintubation in at-risk patients (1, 2, 15). Thus, results must be taken with caution and are not representative of patients with acute respiratory failure. This is a major limitation to the generalizability of our observations and hence to the external validity of our study, and further studies are needed to confirm our results in a broad population of patients with acute respiratory failure. Also, the presence of a nasogastric tube could have magnified leaks and biased the comparison. Adding a "without nasogastric tube" set of conditions would therefore have been useful. This would, however, have raised a methodologic issue because the calculation of trigger and cycling off delays as well as of the prevalence of asynchronies would have been difficult without the EAdi recording.

Table 4. Asynchrony events

Asynchronies	Study Period			
	PSV-NIV-	PSV-NIV+	NAVA-NIV-	NAVA-NIV+
Asynchrony index (%)	40.2 (19.9–51.5)	26.3 (20.7–31.1)	9.0 (4.8–15.8)[ab]	10.8 (8.6–15.0)[ab]
Asynchrony index leaks (%)	11.2 (4.9–28.0)	4.3 (1.8–11.6)	0.0 (0.0–0.7)[ab]	0.0 (0.0–1.2)[ab]
Ineffective efforts, $n.min^{-1}$	0.0 (0.0–0.0)	0.1 (0.0–0.2)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Late cycling, $n.min^{-1}$	2.1 (0.5–4.8)	0.5 (0.2–1.2)	0.0 (0.0–0.0)[ab]	0.0 (0.0–0.0)[ab]
Total of double triggering, $n.min^{-1}$	1.3 (0.7–1.6)	0.7 (0.3–1.0)	0.6 (0.4–1.9)	1.2 (0.6–2.4)[b]
Double triggering type I, $n.min^{-1}$	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.2 (0.0–0.5)[ab]	0.2 (0.0–0.3)[ab]
Double triggering type II, $n.min^{-1}$	1.3 (0.7–1.6)	0.7 (0.3–1.0)	0.5 (0.3–1.5)	0.9 (0.5–1.5)
Premature cycling, $n.min^{-1}$	3.3 (1.4–4.7)	3.8 (2.9–5.5)	0.6 (0.5–1.2)[b]	1.5 (0.7–1.8)[v]
Autotriggering, $n.min^{-1}$	0.3 (0.0–0.6)	0.1 (0.0–0.4)	0.0 (0.0–0.2)	0.0 (0.0–0.2)

PSV-NIV+ and PSV-NIV–, pressure support ventilation with and without noninvasive ventilation algorithm, respectively; NAVA-NIV+ and NAVA-NIV–, neurally adjusted ventilatory assist with and without noninvasive ventilation algorithm, respectively.

All values median (25–75 interquartile range).

Third, we included all the respiratory cycles in the analysis of the NAVA periods, including those that were pneumatically triggered (15% in NAVA-NIV+ and 6% in NAVA-NIV–). This may well have led us to underestimate the beneficial effect of NAVA, but does reflect the real world of daily clinical practice. Furthermore, caution is needed before extrapolating our results because the study is monocentric and pertains to a population limited in size. In addition, the Servo-i has one of the most efficient NIV algorithms in terms of leak compensation; our results might therefore not apply to other NIV algorithms (29). Finally, although we set the NAVA gain according to the manufacturer's procedure and to previous studies (9, 10) (which ensured similar P_{peak} in the four conditions), we cannot be sure that the level of assistance was actually similar among the four conditions. However, major descriptors of breathing pattern such as neural and ventilator inspiratory time as well as EAdi were stable among the four conditions. Only expiratory tidal volume was lower in NAVA than in PSV, as had been previously observed in intubated patients (Table 3) (8, 10).

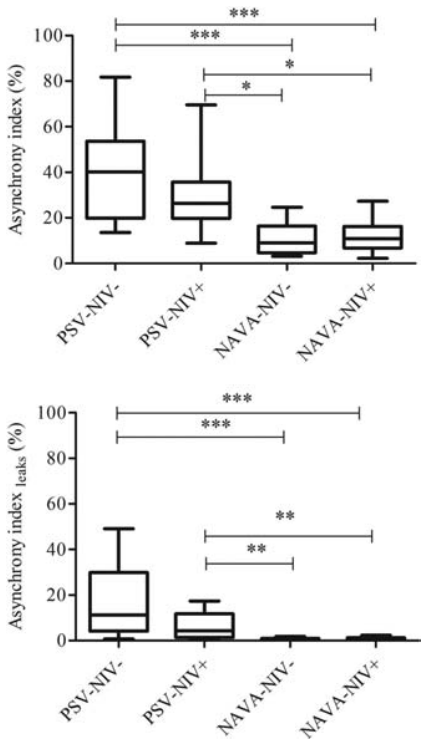

Figure 3. Impact of ventilator mode and noninvasive ventilation algorithm on asynchrony indices. The number of each type of asynchrony is reported as the total number of each event per minute. *AI*, asynchrony index = (number of asynchrony events/[ventilator respiratory rate + ineffective efforts]) × 100; AI_{leaks}, AI specific to leaks = ([autotriggering + ineffective effort + late cycling]/[ventilator respiratory rate + ineffective efforts]) × 100. Data are whiskers: minimum to maximum. $*p < .05$; $**p < .01$; $***p < .001$. *PSV-NIV+*; pressure support ventilation with noninvasive ventilation algorithm; *PSV-NIV–*, pressure support ventilation without noninvasive ventilation algorithm; neurally adjusted ventilatory assist with noninvasive ventilation algorithm, *NAVA-NIV–*; neurally adjusted ventilatory assist without noninvasive ventilation algorithm.

CONCLUSIONS

NIV algorithms achieved their main goal, namely they reduced the level of leaks in both NAVA and PSV. Significantly, the level of leaks was higher than had previously been reported (5, 7), probably as a result of the nasogastric probe. However, despite this beneficial effect and an improvement of Ti_{excess}, the NIV algorithm failed to improve Td_{insp} and to dramatically reduce asynchronies. Eventually, NAVA improved significantly both Td_{insp} and AI. Finally, the combination of NAVA and an NIV algorithm offered the best compromise between a good patient–ventilator synchrony and a low level of leaks.

Whether these results will have an impact on clinical practice remains to be determined. Optimizing patient–ventilator interaction is actually a major goal because patient–ventilator asynchrony is a source of poor NIV tolerance (7), which in turn increases the risk of NIV failure and further intubation (30, 31). The level of leaks is also associated with a higher rate of intubation (30, 31). However, the present study does not address any clinical outcome such as work of breathing, gas exchange, complication rates, or intubation rate. Additional more protracted physiological and clinical studies are now needed to assess the potential clinical benefit of NAVA in patients receiving NIV.

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Chapitre 3

En comparaison avec la ventilation assistée, la PAV et le NAVA préviennent tous deux la surdistension pulmonaire et améliorent de façon similaire le couplage neuro-mécanique.

Comme exposé précédemment (voir supra 3, Des modes de ventilation partielle aux modes de ventilation proportionnelle), la PAV et la NAVA sont deux modes de ventilation dits « proportionnels », définis par une assistance ventilatoire proportionnelle à l'effort instantané du patient. Cette adéquation de l'offre ventilatoire à la demande du patient permet de limiter la surdistension thoracique, d'optimiser l'effort du patient, de restaurer la variabilité cycle à cycle du profil ventilatoire, et d'améliorer la synchronie patient-ventilateur. Tels sont les points communs de ces deux modes. Toutefois, ces deux modes diffèrent par le signal auquel l'assistance ventilatoire est asservie et chacune de ces deux formes d'asservissement possède ses propres limites (voir supra 4 Mode de ventilation proportionnelle et harmonie patient-ventilateur)

Faute d'études à ce sujet, la comparaison entre les modes PAV et NAVA ne pouvait être que théorique.

L'objectif de ce travail a donc été de comparer la PAV et le NAVA chez des patients de réanimation intubés et ventilés.

Seize patients ventilés en VSAI pour insuffisance respiratoire aigue de cause respiratoire ont été inclus. Trois niveaux différents d'assistance (niveaux 50, 100 et 150) ont été successivement déterminés pour chacun de ces modes ventilatoires.

En VSAI, en PAV et en NAVA, le niveau $VSAI_{100}$, PAV_{100}, et $NAVA_{100}$ correspondait, respectivement, au niveau le plus bas permettant d'obtenir un V_T entre 6 et 8 ml/kg de poids idéal. Les niveaux $NAVA_{50}$ et $NAVA_{150}$ correspondaient à 50% et 150% de la valeur du niveau de NAVA en $NAVA_{100}$ tandis que les niveaux PAV_{50} et PAV_{150} correspondaient à 50% et 150% du gain de PAV_{100}. Les 3 modes ont été délivrés dans un ordre aléatoire permettant d'obtenir neuf conditions. Pour chacune de ces conditions, le profil ventilatoire, le délai de trigger inspiratoire, le débit ventilatoire, la pression, l'EAdi, la variabilité cycle à cycle, les gaz du sang et les principales asynchronies patient-ventilateur (appels inefficaces, double déclenchement, auto-déclenchement) ont été mesurés.

Nos résultats ont montré que les modes PAV et NAVA prévenaient tous deux l'augmentation excessive du V_T à des hauts niveaux d'assistance. De plus, le coefficient de variation du V_T était similaire en PAV et en NAVA et plus élevé qu'en VSAI. La prévalence des appels inefficaces était inférieure en PAV et en NAVA alors que plus de doubles déclenchements étaient rapportés en NAVA.

Ce deuxième travail a donc montré que, comparé à la VSAI, la PAV et le NAVA préviennent tous deux la surdistension pulmonaire, restaurent la variabilité cycle à cycle du profil ventilatoire et améliorent de façon identique le couplage neuro-mécanique. Néanmoins, l'impact clinique de cette meilleure synchronie patient-ventilateur reste à être démontré.

Les données issues de ce troisième travail ont été acceptées sous réserve de modifications mineures dans *Critical Care.*

Neurally Adjusted Ventilatory Assist and Proportional Assist Ventilation both improve patient-ventilator interaction.

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ABSTRACT

Introduction: The objective was to compare the impact of three assistance levels of neurally adjusted ventilatory assist (NAVA), proportional assist ventilation (PAV) and pressure support ventilation (PSV) on major features of patient-ventilator interaction.

Methods: PSV, NAVA and PAV were set to obtain a tidal volume (V_T) of 6–8 ml/kg (PSV_{100}, $NAVA_{100}$ and PAV_{100}) in 16 intubated patients. Assistance was further decreased by 50% (PSV_{50}, $NAVA_{50}$ and PAV_{50}) and then increased by 50% (PSV_{150}, $NAVA_{150}$ and PAV_{150}) with all modes. The three modes were randomly applied. Airway flow and pressure, electrical activity of the diaphragm (EAdi) and blood gases were measured. V_T, peak EAdi, coefficient of variation of V_T and EAdi, and the prevalence of the main patient-ventilator asynchronies were calculated.

Results. PAV and NAVA prevented the increase of V_T with high levels of assistance (median 7.4 (interquartile range: 5.7-10.1) $ml.kg^{-1}$ and 7.4 (5.9-10.5) $ml.kg^{-1}$ with PAV_{150} and $NAVA_{150}$ vs. 10.9 (8.9-12.0) $ml.kg^{-1}$ with PSV_{150}, $p<0.05$). EAdi was higher with PAV than with PSV at $level_{100}$ and $level_{150}$. The coefficient of variation of V_T was higher with NAVA and PAV (19 (14-31)% and 21 (16-29)% with $NAVA_{100}$ and PAV_{100} vs. 13 (11-18)% with PSV_{100}, $p<0.05$). The prevalence of ineffective triggering was lower with PAV and NAVA than with PSV ($p<0.05$), but the prevalence of double triggering was higher with NAVA than with PAV and PSV ($p<0.05$).

Conclusions. PAV and NAVA both prevent overdistension, improve neuromechanical coupling, restore the variability of the breathing pattern and decrease patient-ventilator asynchrony in fairly similar ways compared to PSV. Further studies are needed to evaluate the possible clinical benefits of NAVA and PAV on clinical outcomes.

Trial registration: Clinicaltrials.gov NCT02056093. Registered 18 December 2013

Key words: Mechanical ventilation, Patient-ventilator interaction, Neurally adjusted ventilator assist, Proportional assist ventilation, Variability.

Introduction

Partial ventilatory assistance minimizes adverse effects of controlled mechanical ventilation such as excessive sedation and ventilator-induced diaphragm dysfunction (147-149). The most widely used partial ventilatory assistance mode is pressure support ventilation (PSV) (150), in which a constant preset level of pressure assists each inspiration regardless of the patient's inspiratory effort. Mismatching between patient demand and level of assistance is therefore possible and can be potentially harmful: underassistance may induce respiratory discomfort (30) and overassistance may cause lung overdistension and volutrauma (151). Of note, underassistance and overassistance may both generate patient-ventilator asynchrony that is associated with poorer clinical outcomes (53).

Proportional Assisted Ventilation (PAV) and Neurally Adjusted Ventilatory Assist (NAVA) have been designed to overcome this weakness of PSV. These two modes adjust proportionally the amount of assistance delivered. NAVA adjusts ventilator assistance to the electrical activity of the diaphragm (EAdi) recorded with an esophageal catheter (105). PAV adjusts ventilator assistance to the activity of respiratory muscles estimated by an algorithm (104). Previous studies have shown the potential benefits of PAV and NAVA to prevent the risk of overassistance (113, 118, 152, 153), to increase the variability of the breathing pattern (123-125, 127, 133, 134, 154) and to improve patient-ventilator interaction and synchrony (113, 118-121, 130, 131, 146). PAV and NAVA have been previously compared to PSV but not with each other. This comparison would be clinically relevant, as these two modes have their own specific strengths and weaknesses (104, 155).

In the study reported here, we hypothesized that PAV and NAVA improve patient-ventilator interaction in similar ways. The aim of this study was therefore to compare, in patients recovering from acute respiratory failure, the respective impact of various levels of NAVA, PAV and PSV on four major features of patient-ventilator interaction: 1) breathing

pattern, including prevention of overassistance 2) respiratory drive, 3) breathing pattern variability, 4) and patient-ventilator synchrony.

Trial registration: Clinicaltrials.gov NCT02056093. Registered 18 December 2013

Patients and methods

The study was conducted over a period of 3 months in a 10-bed Intensive Care Unit (ICU) in an 1800-bed university hospital. The protocol was approved by the *Comite de Protection des Personnes* Ile de France VI. Informed consent was obtained from patients or relatives.

Patients

Patients initially intubated and ventilated in the ICU were eligible for inclusion in the study if: 1) they had been ventilated for acute respiratory failure *via* an endotracheal tube for more than 48 hours, 2) the condition that had required mechanical ventilation had improved (in particular, ability to trigger the ventilator with an FiO_2 of ≤ 50% and positive end-expiratory pressure (PEEP) ≤ 5 cmH_2O), 3) sedation had been stopped for more than 6 hours, 4) hemodynamic stability was achieved without vasopressor or inotropic medication. Exclusion criteria were known or suspected phrenic nerve dysfunction or other neuromuscular disorders that may involve the diaphragm or impair respiratory drive. Patients with contraindications to EAdi catheter placement (e.g., gastroesophageal varices or obstruction, recent gastroesophageal surgery, facial surgery or trauma, or upper gastrointestinal bleeding) were excluded. Patients in whom the decision to withhold life-sustaining treatment had been made were also ineligible for inclusion.

Ventilation equipment

The conventional nasogastric tube was removed and replaced by a 16 Fr EAdi catheter (Maquet Critical Care, Solna, Sweden) and its position was controlled according to the manufacturer's recommendations (156). PSV and NAVA were delivered using a Servo-I ventilator (Maquet Critical Care, Solna, Sweden) and PAV+ was delivered using a PB840 ventilator (Covidien, Boulder, CO, USA). Male and female were ventilated with an 8- and 7.5 mm internal diameter endotracheal tube, respectively.

Study protocol

Inspiratory pressure support level was initially titrated to obtain a tidal volume (V_T) of 6 to 8 ml/kg of predicted ideal body weight. Flow-trigger sensitivity was set at the lowest possible level without inducing auto-triggering, and cycling-off was set at 30% of peak inspiratory flow (default value). A high upper pressure limits at 45 cmH_2O was set in PAV and NAVA. This level of assistance was defined as PSV_{100}. Patients were then switched to NAVA and the corresponding NAVA level to obtain a similar V_T of 6 to 8 ml/kg was determined during a 5 minute-period. This NAVA level was termed $NAVA_{100}$. Patients were finally switched to PAV and the percentage unloading (%Assist) was set to also obtain a similar V_T of 6 to 8 ml/kg. This %Assist corresponded to PAV_{100}. In each of the three modes, the assist level was further decreased by 50%, corresponding to PSV_{50}, $NAVA_{50}$ and PAV_{50} and then increased by 50%, corresponding to PSV_{150}, $NAVA_{150}$ and PAV_{150}. In the results section, $PSV_{100,}$ $NAVA_{100}$ and PAV_{100} define a medium assistance level also termed $level_{100}$; $PSV_{50,}$ $NAVA_{50}$ and PAV_{50} define a low assistance level also termed $level_{50}$; and $PSV_{150,}$ $NAVA_{150}$ and PAV_{150} define a high assistance level also termed $level_{150}$. Of note, inspiratory pressure support level in PSV_{50} could not be lower than 7 cmH_2O.

Positive end-expiratory pressure (PEEP) and inspired oxygen fraction (FiO_2) were maintained constant throughout the study period at the values in use prior to patient enrolment. The endotracheal tube was suctioned before the beginning of each trial. Each patient underwent three 30-min trials, in each mode, consisting of 20-min stabilization followed by 10-min recording stored on a computer for further analysis. The three modes were applied in computer-generated random order. At the end of each trial, arterial blood was sampled for gas analysis (Radiometer ABL 330, Tacussel, Copenhagen, Denmark) via a catheter and dyspnea was rated using a visual analog scale when possible.

Data acquisition

Flow was measured with a heated Fleisch pneumotachograph, (dead space 51 mL, Hans Rudolph, Kansas City, MO, USA) and airway pressure was measured by a pressure transducer (DP 15-32, Validyne, Northridge, CA, USA) for all modes. Also for all modes, the digital EAdi signal was recorded by an EAdi catheter connected to a Servo-i ventilator (whether the patient was assisted by this ventilator or not) and further converted into an analog signal by a digital-analogic signal converter (National Instruments, Austin, TX, USA). Indeed, during all three modes of ventilation, the EAdi waveform was simultaneously recorded with flow and airway pressure from the respective ventilator. All signals were digitized at a 100-Hz sampling rate (PowerLab/4SP, ADInstruments, Castle Hill, Australia) and recorded on a personal computer for subsequent analysis (Chart software, ADInstruments, Castle Hill, Australia).

Data analysis

Respiratory Parameters and Breathing Pattern. Neural respiratory rate (RR), V_T, duration of pneumatic inspiration (Ti), maximum EAdi, ($EAdi_{max}$), area under the curve of EAdi during inspiratory time ($EAdi_{AUC}$, integrated from baseline to peak), and the V_T-(mL.kg^{-1})/$Eadi_{max}$ ratio were calculated offline from the 10-min airway flow and EAdi recordings. The coefficient of variation (standard deviation divided by the mean) for both flow (CV_{VT}) and EAdi-related variables ($CV_{EAdimax}$) was calculated. Maximum (P_{max}) and mean inspiratory airway pressure (P_{mean}) were measured and calculated from airway pressure recordings.

Patient-ventilator asynchrony. The inspiratory trigger delay was calculated as the time difference between the beginning of the increase in the EAdi signal and the beginning of the ventilator inspiratory flow. Using the EAdi waveform, we quantified the three main types of aynchronies accordingly to previously published definitions (53, 130) (see also Additional File 1): 1) ineffective efforts; 2) auto-triggering and 3) double triggering. Of note, only type

II double triggering defined as one neural inspiration triggering two breath cycles were considered (130). An additional Figure file shows this more in details (see additional File 2). The number of each type of asynchrony was reported as the total number of each event per minute. A global asynchrony index (AI) was computed (53).

Statistical analysis

Statistical analysis was performed with Prism 4.01 software (GraphPad Software, San Diego, CA, USA). Normality testing failed for all results (Kolmogorov-Smirnov). Results are therefore expressed as median (25-75 interquartile range). Within each of the three assistance level groups (i.e $level_{50}$, $level_{100}$ and $level_{150}$), Friedman ANOVA for repeated measures was performed to compare breathing pattern, variability, prevalence of the main asynchronies and blood gases measured with PAV, NAVA and PSV, respectively. Comparison between the three modes was followed, when appropriate, by a pairwise comparison using Dunn's post-hoc test. Linear regression analysis was performed between $EAdi_{max}$ and P_{max} in all conditions and the determination coefficient (R^2) was calculated. Differences were considered significant when the probability p of a type I error was less than 5%.

Results

The study pertains to a convenience sample of sixteen patients (10 males). Their main characteristics and the precipitating factor of acute respiratory failure are summarized in Table 1. Respective assistance levels used for each mode are reported in Table 2. Of note, three patients had chronic obstructive pulmonary disease (COPD) (patients #5, #7 and #16).

Breathing pattern and electrical activity of the diaphragm.

Group median values for representative breathing pattern variables are provided in Figure 1 and Figure 2 (see also Table 3). Inspiratory pressure for each patient under all conditions are displayed in Additional File 3**.** Median airway pressure was similar among $level_{100}$ and $level_{150}$ groups. Within all assistance levels ($level_{50}$, $level_{100}$, $level_{150}$), P_{max} was higher with NAVA than with PAV and PSV (p=0.001; Figure 1, Table 3). In addition, as illustrated in the Figure 3, a strong relation between P_{max} and $EAdi_{max}$ was noted in both NAVA and PAV, whereas no correlation was noted in PSV. At $level_{50}$ and $level_{100}$, V_T was similar among modes. However, at a high assistance level, V_T was significantly higher with PSV_{150} than with $NAVA_{150}$ and PAV_{150} ($p<0.05$). Tidal volume was similar with NAVA and PAV regardless of the assistance level. Inspiratory time and RR remained similar within all modes and at each level of assistance. Of note, at $level_{100,}$ and $level_{150}$, $EAdi_{max}$ and $EAdi_{AUC}$ were higher in PAV than in PSV (Figure 2; Table 3). Whereas the $V_T/EAdi_{max}$ ratio was similar among groups at $level_{50}$, it was higher with PSV than with PAV at $level_{100}$ and $level_{150}$ ($p <0.0001$). In addition, the $V_T/EAdi_{max}$ ratio was higher with PSV than with NAVA at $level_{150}$ ($p <0.0001$). Of note, $V_T/EAdi_{max}$ did not differ between PAV and NAVA regardless of the assistance level.

Breath-by-breath variability

Group median values for coefficient of variation V_T and $EAdi_{max}$ are provided in Figure 4 (see also Additional File 4). The coefficient of variation of V_T was higher with PAV and

NAVA than with PSV at $level_{100}$ and $level_{150}$ ($p<0.05$), while the coefficient of variation of V_T was similar between NAVA and PAV at each level of assistance. Conversely, the coefficient of variation of $EAdi_{max}$ did not change according to ventilator mode and level of assistance, except at $level_{150}$ where it was lower with PAV_{150} than with PSV_{150}.

Patient-ventilator interaction

Table 4 and additional File 5 show the inspiratory trigger delay and the prevalence of patient-ventilator asynchrony in each condition. Inspiratory trigger delay was significantly lower in NAVA than in PAV and PSV at $level_{100}$ and $level_{150}$, respectively. At each level of assistance, almost no ineffective efforts were reported with PAV and NAVA, while the ineffective efforts were detected with PSV at a higher level ($p<0.05$). Inversely, while very few double triggering events were observed with PSV and PAV, the prevalence of double triggering was significantly higher with NAVA ($p<0.05$, Table 4). Type II double triggering was due to ventilator cycled off when the EAdi dropped to 70% of its peak, followed by a rebound in inspiratory flow, cause of the re-triggering, when cycled off to PEEP (see Additional File 2).

No autotriggering was observed in any condition. Overall, the asynchrony index was significantly lower with PAV_{50} and PAV_{100} than with $NAVA_{50}$ and $NAVA_{100}$, respectively ($p<0.05$). Of note, only 2 patients exhibited an AI>10% in PSV_{150}, mostly due to a high number of ineffective efforts (patients #7 and #14). Dyspnea was able to be evaluated in only two patients due to insufficient cooperation (data not shown).

Gas exchange

Neither the mode (PSV, NAVA, PAV) nor the level of assistance ($level_{50,100,150}$) influenced PaO_2, $PaCO_2$ or pH, which remained not significantly different between all conditions, except for $PaCO_2$ that was higher and pH that was lower with PAV_{100}, than with $NAVA_{100}$ (see Additional File 6 for detailed blood gas values).

Discussion

The main findings of our study are as follows: 1) PAV and NAVA both prevented overassistance-induced hyperinflation, in contrast with PSV; 2) PAV and NAVA restored a comparable level of breathing pattern variability that was greater than the variability observed with PSV; 3) Regardless of the level of assistance, PAV and NAVA induced less patient-ventilator asynchrony than PSV, with the exception of double triggering, which was more frequent with NAVA. The similarities observed between NAVA and PSV in terms of breathing pattern, variability and asynchrony are consistent with the conceptual similarities of these two modes.

Breathing pattern and central respiratory neural output

Increasing PSV assist levels were associated with increasing V_T values, in keeping with previous data (37, 157). In contrast, V_T remained stable with NAVA and PAV, despite increasing assist levels (118, 132), suggesting that these modes protect against overdistension. With PSV, the end of the patient's inspiratory effort does not determine cycling-off of the ventilator. A patient may therefore trigger a PSV breath with a small inspiratory effort, then relax, and be passively insufflated. If this breath is given at an excessive assist level, the insufflation may continue while the patient has already stopped inspiring. In contrast with PSV, NAVA and PAV deliver an insufflation that stops when either the output of the inspiratory centers to the diaphragm ends, in the case of NAVA (12), or when the inspiratory muscle activity ends, in the case of PAV.

In addition, because overdistension contributes to downregulate the activity of respiratory control centers (29), tidal volume is maintained constant with PAV and NAVA but not with PSV. The robustness of this protective biofeedback provided by proportional modes as opposed to PSV is illustrated in the present study by the marked alteration of the

coupling between VT and $EAdi_{max}$ (i.e higher VT /EAdi ratio) observed with PSV at high levels of assistance (see Figure 2), which was not observed with the two proportional modes.

Breath-by-breath variability

Fluctuations in the resting breathing pattern of healthy humans have been known for a long time (158). Breathing pattern variability seems to originate from the activity of central pattern generators (91). It is further influenced by the load–capacity relationship of the respiratory system: the higher the loading, the lower the variability (134, 159, 160).

In the present study, the variability of VT with NAVA and PAV was greater than with PSV at each assistance level. In contrast, the variability of EAdi was similar between the three modes, except at high assistance level. These data indicate that the increase in breath-to-breath variability observed during NAVA and PAV is actually due to "unmasking" of the underlying variability in central respiratory neural output and is a direct result of improvement of neuromechanical coupling. To our knowledge, these data, previously described in NAVA (134) have never been described with PAV. They suggest that PAV and NAVA both improve neuromechanical coupling in similar ways.

Patient-ventilator interaction

As previously observed, NAVA and PAV improved patient-ventilator synchrony as compared to PSV (118-121, 130, 132). Although inspiratory trigger delays in all modes were consistently greater than previously reported (112, 113, 161), lower inspiratory trigger delays seemed to be more frequently noted in NAVA. The wide variability of the trigger delays (see additional File 5) and their higher values can be ascribed to the fact that we used two different ventilators instead of one, that various levels of assist were delivered, by the experimental settings itself, and by the various precipitating factors of acute respiratory failure in our patients.

It is noteworthy that, in the present study, PAV and NAVA provided a similar benefit on ineffective triggering. This can be interpreted as a consequence of the trigger by the EAdi in NAVA, and a better neuromechanical coupling in PAV that may prevented chest hyperinflation, a major risk factor for ineffective triggering (53). As we have observed in a previous study that the two proportional modes prevent lung overdistension to an equivalent degree, it is not surprising that both modes induced a similar decrease in the prevalence of patient-ventilator asynchrony.

Two types of double triggering have been described in NAVA (130). Type I double triggering is the result of a biphasic EAdi signal but its significance is unknown, which is why, strictly speaking, it cannot be considered to be patient–ventilator asynchrony. With type II double triggering, however, one neural inspiration triggers two breaths, which corresponds to real asynchrony. We therefore only considered type II double triggering in the present study and observed that this asynchrony was significantly more frequent with NAVA than with PSV and PAV. However, the relevance of this asynchrony has yet to be determined (130).

Limitations of the study

Our study has several limitations. Firstly, as patients at high-risk of asynchrony (e.g. difficult-to-wean or severe COPD patients) were not specifically selected in this study (53) and because we targeted a V_T of 6-8 ml/kg in $level_{100}$ (162), a very low incidence of asynchrony was observed with all modes and conditions. This study may therefore have underestimated the benefits of NAVA and PAV (111, 123, 163, 164), but we deliberately decided to compare these modes in patients in the recovery phase after acute respiratory failure encountered in daily practice rather than in a very selected population, with the risk of showing results that would only be transposable to a niche population. Secondly, the trials in our study were probably not sufficiently long to allow an improvement of gas exchange. This

might be a reason why, despite a greater variability of the breathing pattern in PAV and NAVA, no impact on PaO_2 was observed in contrast with previously published results (133). Thirdly, the choice of a resulting V_T of 6-8ml/kg to match the assistance $level_{100}$ with the three modes may be questionable. Indeed, a poor correlation between V_T and PAV %Assist (165) as well as NAVA level (166) has been reported. In addition, the high V_T variability may have jeopardized the accuracy of its setting. However, the fact that we observed a comparable P_{mean} with the three modes at assistance $level_{100}$ suggests that the patients received a comparable level of assistance. Fourthly, because we focused on patients in the recovery phase after acute respiratory failure and because PSV_{50} could not be lower than 7 cmH_2O, PSV_{100} settings could sometimes be very close to PSV_{50}. Fifthly, for technical reasons we were not able to provide comparisons of cycling off delays within the three modes. Finally, contrary to the sequence of the ventilatory modes tested, the sequence of the level of assistance was not randomized. Therefore, we cannot rule out a potential time effect.

Clinical implications

Most of our findings are potentially clinically relevant. Lung-protective ventilation has become a major concern in ICU patients, even in those without acute respiratory distress syndrome (167, 168). Preventing alveolar overdistension and subsequent volotrauma caused by lung hyperinflation is now a major therapeutic goal. In this respect, NAVA and PAV provide an interesting tool to prevent overassistance-induced hyperinflation.

Variability of breathing pattern has become a matter of concern in ICU patients, as a recent study showed that a higher variability of respiratory rate was associated with better prognosis (169). In addition, a more variable breathing pattern is associated with better pulmonary function in animal models of lung injury (170-174). Finally, severe patient-ventilator asynchrony is associated with longer duration of mechanical ventilation and a

greater need for tracheostomy (53). Of note, patient-ventilator asynchrony may be either a cause or a consequence of the severity of the respiratory disease requiring mechanical ventilation. Whether optimization of ventilatory settings, by using PAV or NAVA, can shorten the duration of mechanical ventilation by reducing the incidence of asynchrony has therefore not been demonstrated.

Conclusion

In conclusion, PAV and NAVA both prevents overdistension and improves neuromechanical coupling and patient-ventilator asynchrony in fairly similar ways compared to PSV. Further studies are needed to evaluate the possible clinical benefits of NAVA and PAV on clinical outcomes, especially in the recovery phase of acute respiratory failure.

List of abbreviations

AI: asynchrony index
CV: coefficient of variation
$CV_{Eadimax}$: coefficient of variation of $EAdi_{max}$
EAdi: electrical activity of the diaphragm
$EAdi_{max}$: maximum electrical activity of the diaphragm
$EAdi_{AUC}$: integrated EAdi activity
NAVA: neurally adjusted ventilatory assist
PAV: proportional assisted ventilation
PEEP: positive end-expiratory pressure
P_{max}: peak airway pressure
PSV: pressure support ventilation
RR: respiratory rate
Ti: inspiratory time
V_T: tidal volume

Competing interest

The *Association pour le Développement et l'Organisation de la Recherche en Pneumologie*, a non-profit structure that supports the research activities of the "Service de Pneumologie et Réanimation Médicale, Groupe Hospitalier Pitié-Salpêtrière", has received an unrestricted research grant from Maquet France SA, Orléans, France (2009), and Covidien, Dublin, Ireland (2013) to support pathophysiological research studies on NAVA and PAV, respectively. A. Demoule is the principal investigator of a study on NAVA, has been a consultant for Covidien and has given lectures for Covidien and Maquet. The others authors have no conflict of interest.

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Figure 1. Impact of ventilator mode and level of assistance on mean (P_{mean}) and maximum airway pressure (P_{max}).

Pressure support ventilation $(PSV)_{100}$, neurally adjusted ventilatory assist $(NAVA)_{100}$, and proportional assist ventilation $(PAV)_{100}$ are medium levels of assistance set to obtain a tidal volume (VT) between 6 and 8 $mL.kg^{-1}$ ideal body weight. PSV_{50}, $NAVA_{50}$ and PAV_{50} are low levels of assistance defined by decreasing the assistance level by 50% in each condition. Inversely, PSV_{150}, $NAVA_{150}$ and PAV_{150} are defined by increasing the assistance level by 50% in each condition.

* $p < 0.05$ with PSV; $^{£}$ $p < 0.05$ with NAVA. Data are expressed as median and interquartile range.

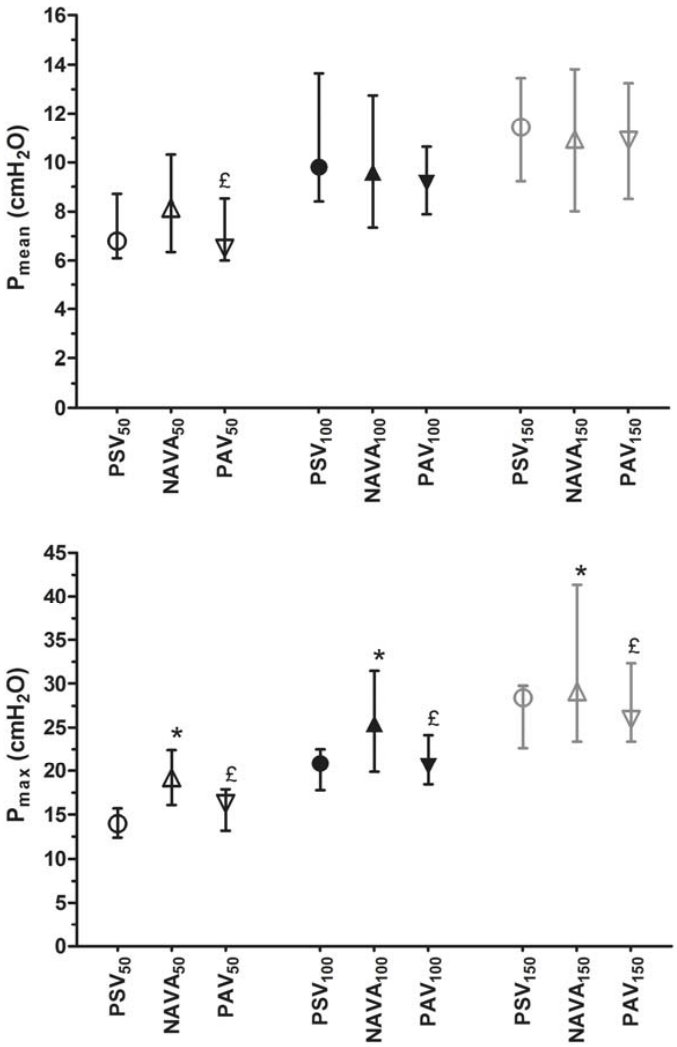


Figure 2. Impact of ventilator mode and level of assistance on the major descriptors of breathing pattern and diaphragmatic electrical activity (EAdi).

Pressure support ventilation $(PSV)_{100}$, neurally adjusted ventilatory assist $(NAVA)_{100}$, and proportional assist ventilation $(PAV)_{100}$ are medium levels of assistance set to obtain a tidal volume (V_T) between 6 and 8 $mL.kg^{-1}$ ideal body weight. PSV_{50}, $NAVA_{50}$ and PAV_{50} are low levels of assistance defined by decreasing the assistance level by 50% in each condition. Inversely, PSV_{150}, $NAVA_{150}$ and PAV_{150} are defined by increasing the assistance level by 50% in each condition.

$EAdi_{max}$, peak of EAdi; *RR*, respiratory rate; $V_T/Eadi_{max}$, neuromechanical coupling.

* $p < 0.05$ with PSV. Data are expressed as median and interquartile range.

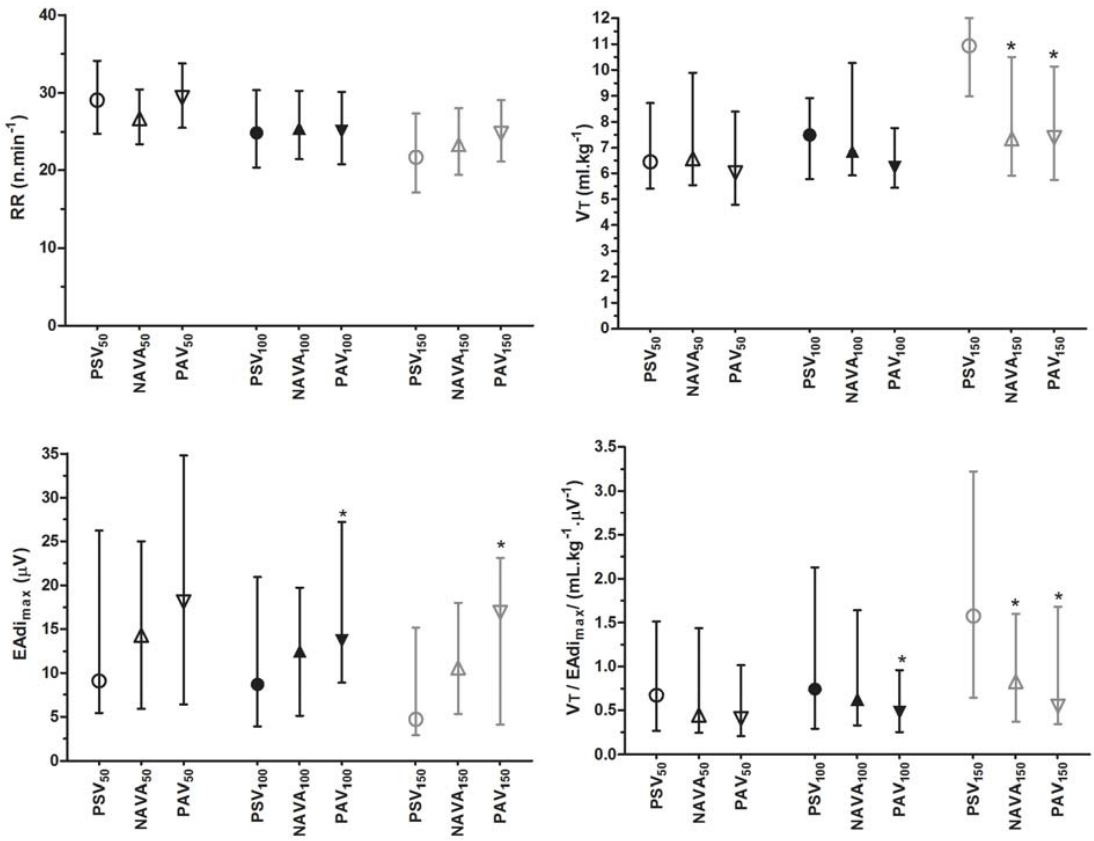
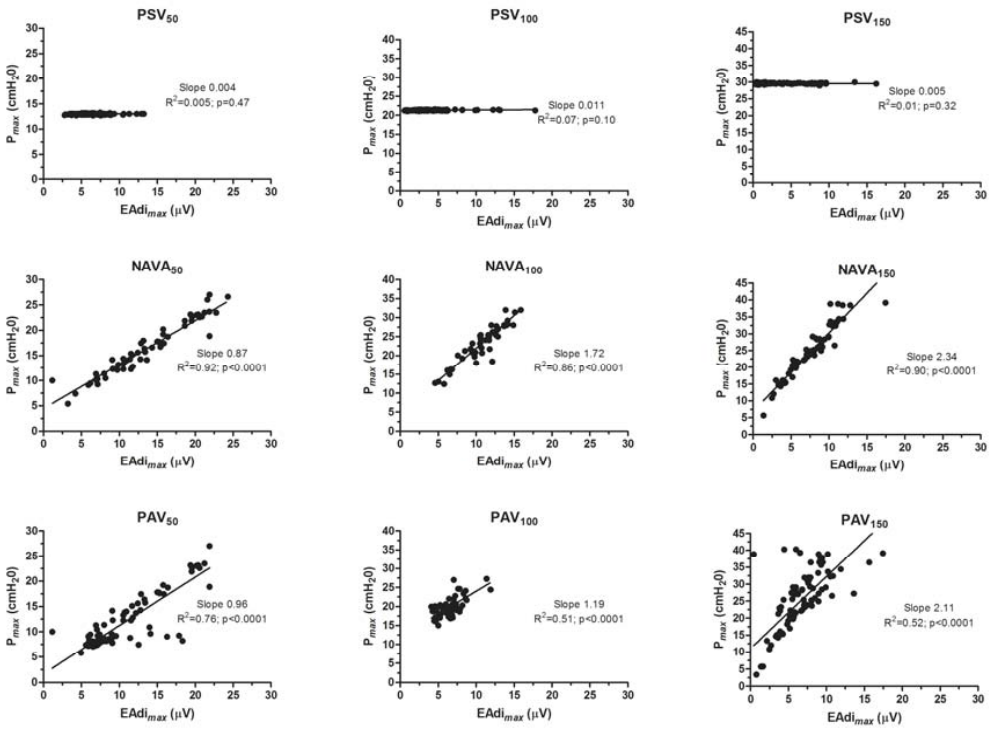


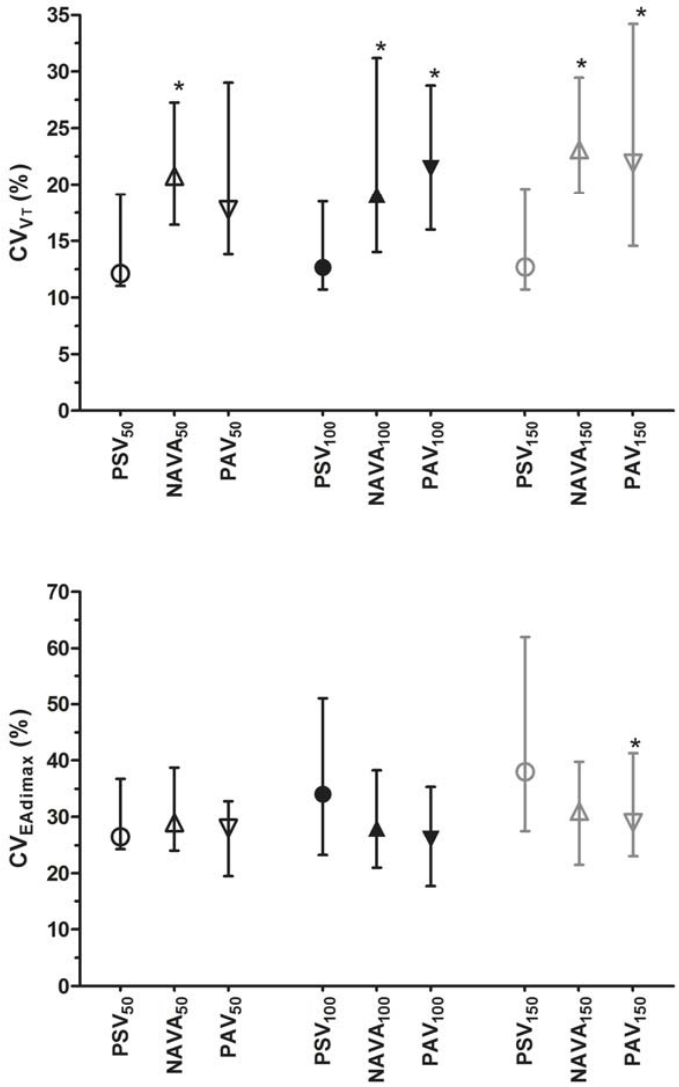
Figure 3. Relationships between maximum airway pressure (P_{max}) and peak of diaphragmatic electrical activity ($EAdi_{max}$) in the three modes and in all conditions.



Note the strong correlation between $EAdi_{max}$ and P_{max} in PAV and NAVA whereas no correlation was found in PSV.

Figure 4. Impact of ventilator mode and level of assistance on the coefficient of variation of tidal volume (CV_{VT}) and maximum electrical activity of the diaphragm ($CV_{EAdimax}$).

Pressure support ventilation $(PSV)_{100}$, neurally adjusted ventilatory assist $(NAVA)_{100}$, and proportional assist ventilation $(PAV)_{100}$ are medium levels of assistance set to obtain a tidal volume (VT) between 6 and 8 $mL.kg^{-1}$ ideal body weight. PSV_{50}, $NAVA_{50}$ and PAV_{50} are low levels of assistance defined by decreasing the assistance level by 50% in each condition. Inversely, PSV_{150}, $NAVA_{150}$ and PAV_{150} are defined by increasing the assistance level by 50% in each condition.



* p <0.05 with PSV; £ p <0.05 with NAVA; Data are expressed as median and interquartile range.

Tables

Table 1: Patient characteristics at enrolment.

Patient No.	Age (years)	BMI ($kg.m^{-2}$)	SAPS 2	Admission diagnosis	MV duration before inclusion (days)	FiO_2	PEEP (cmH_2O)
1	70	32.0	61	Pneumonia	8	0.5	4
2	90	29.9	63	ARDS	2	0.4	5
3	83	16.0	55	ARDS	6	0.5	4
4	67	37.6	56	Pneumonia	12	0.5	5
5	77	27.8	47	Acute respiratory failure due to decompensation of COPD	7	0.5	4
6	60	27.5	35	Pneumonia	8	0.5	4
7	60	25.0	26	Acute respiratory failure due to decompensation of COPD	7	0.5	4
8	81	33.2	49	Pneumonia	4	0.4	4
9	74	18.4	63	Pneumonia	6	0.5	4
10	64	23.5	97	Pneumonia	11	0.5	5

11	67	23.0	51	ARDS	12	0.5	4
12	62	22.8	84	ARDS	7	0.5	4
13	62	25.0	49	Pneumonia	2	0.5	5
14	66	29.4	67	Acute respiratory failure due to decompensation of COPD	21	0.5	5
15	65	26.0	72	Pneumonia	12	0.5	5
16	67	31.6	46	Pneumonia	2	0.4	5
Median (IQR)	**67 (63-75)**	**27 (23-30)**	**55 (48-64)**		**7.0 (5.5-11.0)**	**0.5 (0.5-0.5)**	**4 (4-5)**

Definition of abbreviations: M, male; F, female; BMI, body mass index; SAPS II, Simplified Acute Physiology Score II; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; IQR, interquartile range; ARDS, acute respiratory distress syndrome, COPD, chronic obstructive pulmonary disease.

Table 2. Assistance levels in each experimental condition.

Mode, assistance setting	$Level_{50}$	$Level_{100}$	$Level_{150}$	Notes
PSV, inspiratory pressure (cmH_2O)	7.0 (7.0-7.2)	14.0 (11.5-15.2)	21.0 (17.2-21.7)	*The inspiratory pressure support level, set by the clinician, is kept constant regardless of the mechanical properties of the lung/thorax and patient effort.*
NAVA, NAVA level ($cmH_2O/\mu V$)	0.6 (0.4-0.9)	1.3 (0.8-1.8)	1.9 (1.2-2.7)	*The NAVA level is a proportional gain factor expressed in cmH2O/µV of EAdi. It represents the magnitude (in cmH2O) of positive airway pressure applied per µV EAdi during the course of each inspiration.*
PAV, proportion of assistance (%)	27 (25-35)	55 (50-70)	82 (75-95)	*The proportion of assistance is the percentage of work provided by the ventilator. The rest of the work is provided by the patient.*

EAdi, electrical activity of the diaphragm; *PSV,* pressure support ventilation*; NAVA,* neurally adjusted ventilatory assist; *PAV*, proportional assist ventilation.

Data are provided as median (interquartile range)

Table 3. Impact of ventilator mode and level of assistance on the main descriptors of breathing pattern and electrical activity of the diaphragm (EAdi)

	PSV	NAVA	PAV
P_{mean} (cmH_2O)			
$level_{50}$	6.8 (6.1-8.7)	8.1 (6.3-10.3)	6.5 (6.0-8.5) £
$level_{100}$	9.8 (8.4-13.6)	9.6 (7.3-12.7)	9.1 (7.9-10.6)
$level_{150}$	11.4 (9.2-13.4)	10.9 (8.0-13.8)	10.9 (8.5-13.2)
P_{peak} (cmH_2O)			
$level_{50}$	13.9 (12.4-15.7)	19.2 (16.1-22.4) *	16.2 (13.1-17.9) £
$level_{100}$	20.8 (17.8-22.5)	25.4 (19.9-31.4) *	20.5 (18.5-24.1) £
$level_{150}$	28.4 (22.6-29.7)	29.1 (23.4-41.3) *	25.9 (23.4-32.3) £
Respiratory rate ($n.min^{-1}$)			
$level_{50}$	30 (25-34)	28 (25-32)	30 (26-34)
$level_{100}$	24 (19-32)	27 (22-30)	28 (17-31)
$level_{150}$	23 (17-25)	25 (20-29)	26 (18-30)
Tidal volume ($mL.kg^{-1}$ IBW)			
$level_{50}$	6.4 (5.4-8.7)	6.6 (5.5-9.9)	6.0 (4.8-8.4)
$level_{100}$	7.5 (5.8-8.9)	6.9 (5.9-10.3)	6.2 (5.4-7.8)
$level_{150}$	10.9 (8.9-12.0)	7.4 (5.9-10.5) *	7.4 (5.7-10.1) *
Minute ventilation ($mL.min^{-1}$)			
$level_{50}$	10.8 (8.9-15.8)	9.8 (8.2-14.4)	11.0 (7.9-14.5)
$level_{100}$	10.6 (8.2-14.1)	10.0 (9.2-16.6)	9.8 (8.0-13.5)
$level_{150}$	12.5 (9.8-17.3)	10.1 (7.8-13.9)	11.3 (8.6-14.5)
Inspiratory time (sec)			
$level_{50}$	0.72 (0.67-0.82)	0.77 (0.60-0.84)	0.73 (0.61-0.99)

$level_{100}$	0.72 (0.67-0.95)	0.78 (0.61-0.93)	0.76 (0.64-1.06)
$level_{150}$	0.85 (0.69-1.18)	0.79 (0.59-0.93)	0.83 (0.64-1.09)
$EAdi_{max}$			
$level_{50}$	9.1 (5.4-26.2)	14.3 (5.9-25.0)	18.1 (6.4-34.8)
$level_{100}$	8.7 (3.9-20.9)	12.5 (5.1-19.7)	13.7 (8.9-27.2) *
$level_{150}$	4.7 (2.9-15.1)	10.6 (5.3-18.0)	10.9 (4.1-13.1) *
$EAdi_{AUC}$			
$level_{50}$	9.5 (3.9-13.6)	9.9 (4.8-16.0)	13.2 (4.7-19.9)
$level_{100}$	7.1 (3.6-13.5)	8.5 (4.9-12.3)	12.2 (6.2-18.8) *
$level_{150}$	4.3 (2.4-8.7)	8.9 (4.4-11.4)	11.4 (3.3-14.5) *
V_T /$EAdi_{max}$			
$level_{50}$	0.67 (0.27-1.51)	0.44 (0.24-1.43)	0.40 (0.20-1.01)
$level_{100}$	0.74 (0.29-2.13)	0.62 (0.33-1.64)	0.47 (0.25-0.96) *
$level_{150}$	1.67 (0.64-3.22)	0.83 (0.37-1.60) *	0.54 (0.34-1.68) *

$EAdi_{max}$, peak EAdi; *$EAdi_{AUC}$*, area under the EAdi curve; *P_{mean}*; mean inspiratory airway pressure; *P_{max}*, maximum inspiratory airway pressure; *PSV*, pressure support ventilation; *PAV*, proportional assist ventilation; *NAVA*, neurally adjusted ventilatory assist.

$Level_{100}$ is a medium assistance level set to obtain a VT of 6–8 $ml.kg^{-1}$ ideal body weight. $Level_{50}$ is a low assistance level defined as $level_{100}$ decreased by 50%. $Level_{150}$ is a high assistance level defined as $level_{100}$ increased by 50%.

Data are provided as median (interquartile range)

Table 4: Impact of ventilator mode and level of assistance on patient-ventilator interaction and asynchrony indices.

	PSV	NAVA	PAV
Inspiratory trigger delay (msec)			
$level_{50}$	162 (109-241)	157 (138-289)	185 (140-305)
$level_{100}$	170 (140-282)	124 (100-238)	224 (176-280) £
$level_{150}$	266 (140-427)	164 (99-278) *	201 (166-317)
Ineffective efforts ($n.min^{-1}$)			
$level_{50}$	0.00 (0.00-0.07)	0.00 (0.00-0.00) *	0.00 (0.00-0.00) *
$level_{100}$	0.03 (0.00-0.26)	0.00 (0.00-0.00) *	0.00 (0.00-0.00) *
$level_{150}$	0.27 (0.01-1.23)	0.00 (0.00-0.00) *	0.00 (0.00-0.00) *
Auto-triggering ($n.min^{-1}$)			
$level_{50}$	0.00 (0.00-0.03)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
$level_{100}$	0.00 (0.00-0.03)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
$level_{150}$	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Double triggering ($n.min^{-1}$)			
$level_{50}$	0.00 (0.00-0.00)	0.42 (0.08-0.50)*	0.00 (0.00-0.00) £
$level_{100}$	0.00 (0.00-0.18)	0.33 (0.10-0.92)*	0.00 (0.00-0.10) £
$level_{150}$	0.00 (0.00-0.21)	0.30 (0.02-0.87)*	0.00 (0.00-0.20) £
Asynchrony index (%)			
$level_{50}$	0.21 (0.00-0.65)	1.41 (0.34-2.91)*	0.13 (0.00-0.44) £
$level_{100}$	0.61 (0.04-1.28)	1.73 (0.38-2.69)	0.00 (0.00-0.58) £
$level_{150}$	1.65 (0.58-5.77)	1.17 (0.05-3.99)	0.19 (0.00-1.12)

PSV, pressure support ventilation*; NAVA,* neurally adjusted ventilatory assist; *PAV*, proportional assist ventilation.

$Level_{100}$ is a medium assistance level set to obtain a VT of 6–8 $ml.kg^{-1}$ ideal body weight. $Level_{50}$ is a low assistance level defined as $level_{100}$ decreased by 50%. $Level_{150}$ is a high assistance level defined as $level_{100}$ increased by 50%.

The number of each type of asynchrony is reported as the total number of each event per minute. Asynchrony index is defined as the total number of asynchrony events x 100/(ventilator respiratory rate + ineffective efforts).

* $p < 0.05$ with PSV; £ $p < 0.05$ with NAVA; data are expressed as median (interquartile range).

ADDITIONAL FILES

Neurally Adjusted Ventilatory Assist and Proportional Assist Ventilation both improve patient-ventilator interaction.

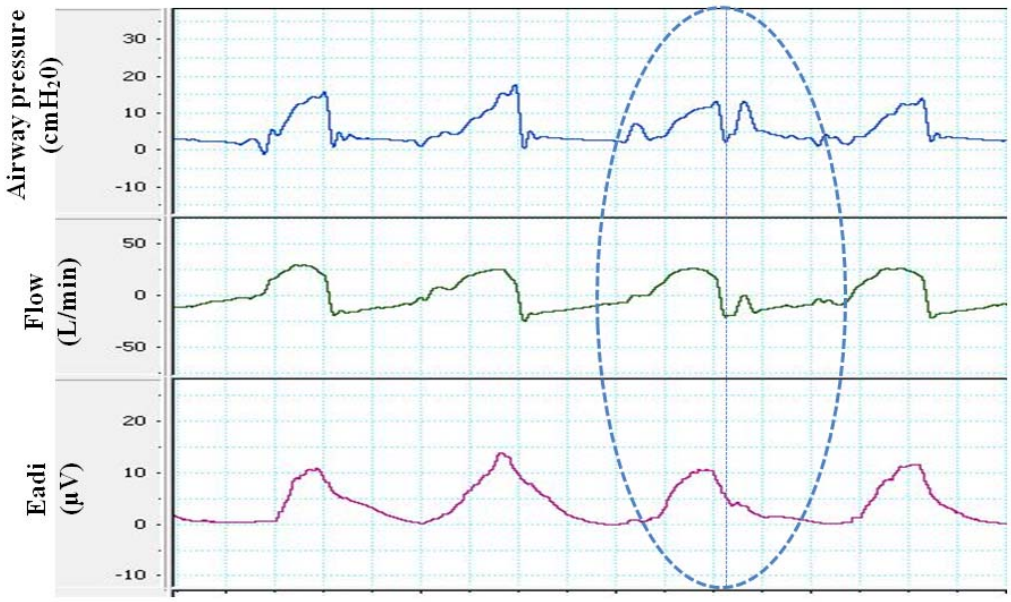
Matthieu Schmidt; Felix Kindler; Jérôme Cecchini; Elise Morawiec; Romain Persichini;

Thomas Similowski, Alexandre Demoule

Additional File 1. Definitions of patient- ventilator interaction indices and the main asynchronies collected

Type of asynchrony	Definitions
Inspiratory trigger delay	Time difference between the beginning of the increase in the EAdi signal and the beginning of the ventilator inspiratory flow
Ineffective effort	Presence of a characteristic electrical activity of the diaphragm not followed by a ventilator-delivered breath
Auto-triggering	A ventilator-delivered breath with no corresponding electrical activity of the diaphragm
Double triggering	The occurrence of two ventilator-delivered breaths separated by an expiratory time less than half of the mean inspiratory time during one single electromyographic activity.
Asynchrony index	(Ineffective efforts + auto-triggering + double triggering) x 100 / (number of breaths + ineffective efforts).

Additional File 2: Example of Type II double triggering under NAVA.



EAdi, electrical activity of the diaphragm.

Note that the ventilator cycled off when the EAdi dropped to 70% of its peak and re-triggered when cycled off to PEEP.

Additional File 3. Inspiratory pressure (cmH_2O) over PEEP for each patient under the three modes and three assist levels

Patient No.	PSV_{50}	$NAVA_{50}$	PAV_{50}	PSV_{100}	$NAVA_{100}$	PAV_{100}	PSV_{150}	$NAVA_{150}$	PAV_{150}
1	13	19	12	21	24	15	29	26	20
2	9	9	7	13	15	11	16	18	16
3	9	13	9	17	20	15	25	22	25
4	7	11	13	12	15	21	18	17	31
5	8	17	14	16	23	16	24	34	19
6	8	12	13	16	17	21	23	20	28
7	9	12	8	16	9	14	23	19	20
8	9	15	15	17	25	17	24	35	18
9	10	17	12	18	30	17	25	38	20
10	10	15	12	18	18	17	25	23	27
11	8	13	12	16	16	16	24	19	20
12	9	21	11	18	28	14	26	28	27
13	7	17	13	9	22	17	14	32	28
14	20	27	27	30	35	36	35	39	38
15	7	21	12	13	36	31	19	32	23
16	7	8	7	8	14	8	12	20	8

PSV, pressure support ventilation*; NAVA,* neurally adjusted ventilatory assist; *PAV*, proportional assist ventilation.

$Level_{100}$ is a medium assistance level set to obtain a VT of 6–8 $ml.kg^{-1}$ ideal body weight. $Level_{50}$ is a low assistance level defined as $level_{100}$ decreased by 50%. $Level_{150}$ is a high assistance level defined as $level_{100}$ increased by 50%.

Additional File 4. Impact of ventilator mode and assistance level on the coefficients of variation of neural respiratory rate, tidal volume and peak electrical activity of the diaphragm ($EAdi_{max}$)

	PSV	NAVA	PAV
Coefficient of variation of Tidal Volume			
$level_{50}$	12.1 (11.0-19.1)	20.7 (16.4-27.3) *	17.7 (13.8-29.0)
$level_{100}$	12.6 (10.7-18.5)	19.1 (14.0-31.2) *	21.4 (16.0-28.7) *
$level_{150}$	12.7 (10.7-19.6)	23.1 (19.2-29.4) *	21.9 (14.5-34.2) *
Coefficient of variation of inspiratory time			
$level_{50}$	11.4 (7.3-18.1)	12.7 (6.2-27.4)	16.8 (7.2-28.2)
$level_{100}$	9.7 (7.7-13.6)	20.4 (10.6-26.7) *	18.3 (7.2-34.5) *
$level_{150}$	13.9 (8.9-31.7)	19.4 (10.6-29.3)	14.0 (5.5-25.0)
Coefficient of variation of neural respiratory rate			
$level_{50}$	10.3 (9.3-20.1)	11.3 (7.8-22.4)	15.1 (8.2-29.7)
$level_{100}$	12.4 (8.7-15.8)	18.0 (11.2-25.9)	17.3 (6.4-29.9)
$level_{150}$	12.9 (9.5-30.6)	18.4 (12.6-34.3)	13.7 (6.6-21.0)
Coefficient of variation of $EAdi_{max}$			
level50	26.5 (24.2-36.7)	29.0 (24.0-38.7)	28.0 (19.5-32.8)
level100	34.0 (23.2-51.0)	28.0 (21.0-38.2)	26.0 (17.7-35.3)
level150	38.0 (27.5-62.0)	31.0 (21.5-39.7)	29.0 (23.0-41.2) *

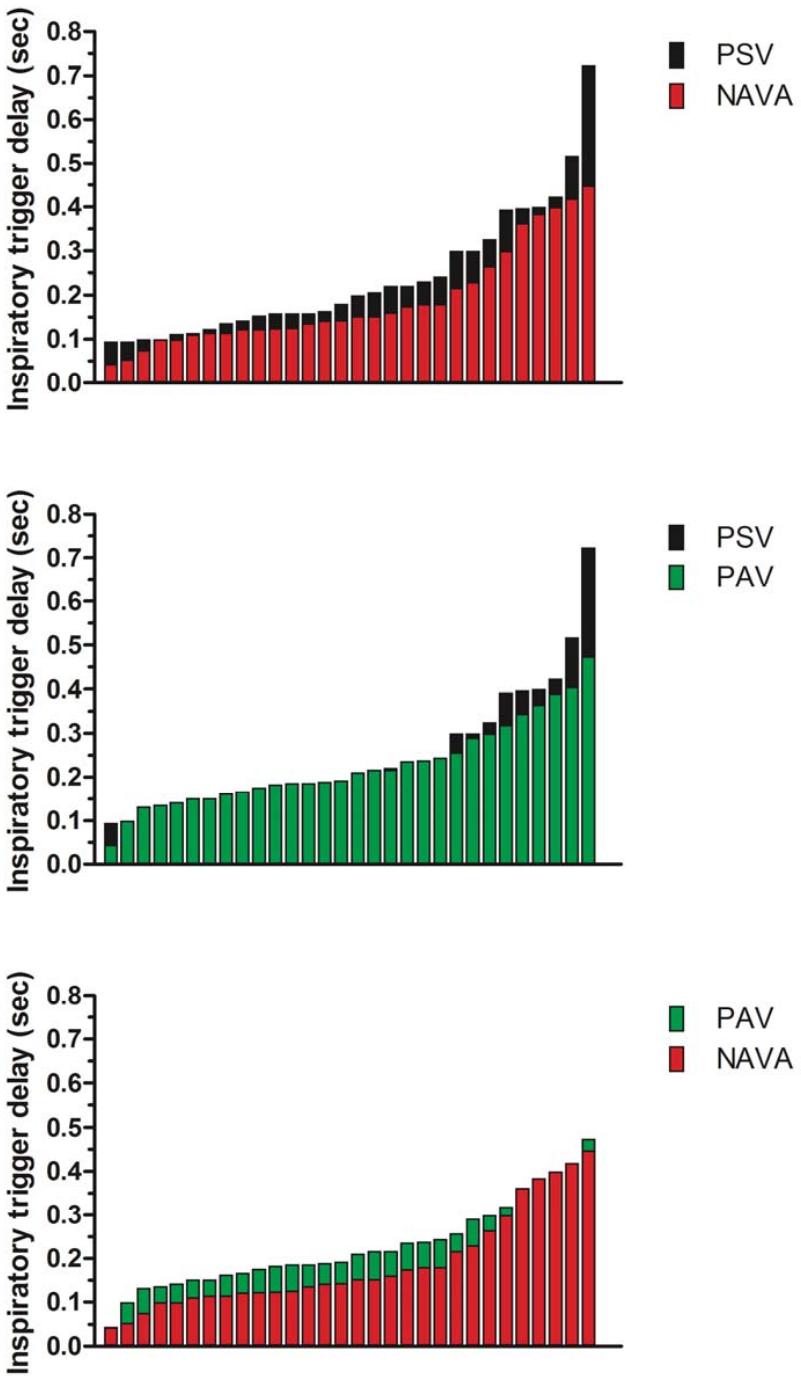
PSV, pressure support ventilation*; NAVA,* neurally adjusted ventilatory assist; *PAV*, proportional assist ventilation.

$Level_{100}$ is a medium assistance level set to obtain a VT of 6–8 $ml.kg^{-1}$ ideal body weight. $Level_{50}$ is a low assistance level defined as $level_{100}$ decreased by 50%. $Level_{150}$ is a high assistance level defined as $level_{100}$ increased by 50%.

* $p < 0.05$ with PSV; data are expressed as median (interquartile range).

Additional File 5: Distribution of the inspiratory trigger delays per mode

PSV, pressure support ventilation*; NAVA*, neurally adjusted ventilatory assist; *PAV*, proportional assist ventilation.



Additional File 6. Impact of ventilator mode and level of assistance on gas exchange.

	PSV	NAVA	PAV
pH			
$level_{50}$	7.38 (7.36-7.43)	7.39 (7.35-7.44)	7.38 (7.33-7.44)
$level_{100}$	7.39 (7.37-7.46)	7.43 (7.35-7.46)	7.38 (7.35-7.44) £
$level_{150}$	7.41 (7.39-7.47)	7.43 (7.36-7.47)	7.39 (7.35-7.48)
PaO_2			
$level_{50}$	78 (74-91)	79 (73-101)	80 (75-90)
$level_{100}$	81 (74-96)	80 (71-95)	78 (74-88)
$level_{150}$	78 (72-94)	79 (71-92)	78 (69-92)
$PaCO_2$			
$level_{50}$	38 (35-49)	39 (34-49)	39 (34-53)
$level_{100}$	37 (33-45)	36 (32-47)	39 (32-48) £
$level_{150}$	36 (32-44)	35 (32-46)	38 (31-47)

PSV, pressure support ventilation*; NAVA,* neurally adjusted ventilatory assist; *PAV*, proportional assist ventilation.

$Level_{100}$ is a medium assistance level set to obtain a VT of 6–8 $ml.kg^{-1}$ ideal body weight. $Level_{50}$ is a low assistance level defined as $level_{100}$ decreased by 50%. $Level_{150}$ is a high assistance level defined as $level_{100}$ increased by 50%.

Blood gases were obtained in 13/16 patients.

* $p < 0.05$ with PSV; £ $p < 0.05$ with NAVA; data are expressed as median (interquartile range).

Chapitre 4

L'EMG de surface des muscles inspiratoires extra-diaphragmatiques pourrait constituer un outil simple et objectif pouvant permettre au clinicien d'optimiser les réglages du ventilateur dans le but de minimiser la dysharmonie patient-ventilateur.

Chez les patients sous assistance ventilatoire mécanique, la dyspnée est fréquente, intense, corrélée à l'anxiété et potentiellement associée à un allongement de la durée de ventilation (30). Dans près d'un tiers des cas, les réglages du ventilateur, qui fréquemment entrainent une « sous-assistance », semblent être impliqués dans la genèse de la dyspnée (5) (Voir infra, Annexe I et II). L'augmentation du niveau d'assistance peut soulager la dyspnée, mais peut paradoxalement générer des phénomènes d'hyperinflation, eux même source d'asynchronies patient-ventilateur. Il est donc nécessaire de trouver des outils pour surveiller les réglages du ventilateur en VSAI. L'activité EMG des muscles inspiratoires extra-diaphragmatiques pourrait en être un. En effet, enregistrer l'activité EMG de ces muscles est simple et faisable en routine en réanimation (136) mais leur utilisation en tant que marqueur dynamique de la dyspnée et des modifications du ventilateur en ventilation invasive n'est pas démontré. Ainsi, dans ce quatrième travail nous avons fait l'hypothèse que l'EMG de surface des muscles scalènes, parasternaux et *Alae Nasi* pourraient remplir cette fonction.

Nous avons donc sélectionné douze patients intubés ou trachéotomisés qui 1) étaient ventilé en VSAI, 2) n'avaient pas reçu de sédatif ou vasopresseur dans les 12 dernières heures et 3) étaient capables de répondre aux ordres simples. Chez ces 12 patients, deux niveaux

d'aide inspiratoire (AI) ont été appliquée : bas et haut pour obtenir respectivement un V_T de 6-8mL/kg et 8-12mL/kg. De même, deux réglages de trigger expiratoire (TE) ont été également été appliqués : bas et haut réglés respectivement à 5% et 30%. Quatre conditions ont ainsi été successivement appliquées dans un ordre aléatoire : AI haute-TE basse ; AI basse-TE basse ; AI haute-TE haut, et AI bas-TE haut. Au cours de ces quatre périodes d'enregistrement, l'EMG de surface des muscles scalènes, parasternaux et *Alae Nasi* (EMG_{max} et EMG_{AUC}), la prévalence des appels inefficaces, l'EVA dyspnée et le score Adaptation to The Intensive Care Environment (ATICE) scale (175) ont été enregistrés.

Pour les trois muscles, l'activité EMG_{max} et EMG_{AUC} étaient significativement supérieures dans les conditions de basse AI, tandis que l'activité EMG était peu influencée par le TE. De même, le rapport EMG_{AUC}/V_T des trois muscles était supérieur dans la condition AI haute-TE basse. Une corrélation forte était retrouvée entre la dyspnée et l'EMG_{max} tandis que la prévalence des appels inefficaces et la dyspnée ou l'EMG_{max} étaient inversement corrélée. .

L'activité EMG des muscles inspiratoires extra-diaphragmatiques pourrait donc être un marqueur de dyspnée en ventilation mécanique. Cette application pourrait être particulièrement intéressante chez les patients non communiquant.

Ce travail a fait l'objet d'une publication scientifique dans *Intensive Care Medicine* (176).

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ORIGINAL

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Abstract *Context:* Pressure support ventilation (PSV) must be tailored to the load capacity balance of the respiratory system. While "over assistance" generated hyperinflation and ineffective efforts, "under assistance" increased respiratory drive and causes dyspnea. Surface electromyograms (sEMGs) of extradiaphragmatic inspiratory muscles were responsive to respiratory loading/unloading. *Objectives:* To determine if sEMGs of extradiaphragmatic inspiratory muscles vary with PSV settings and relate to the degree of discomfort and the intensity of dyspnea in acutely ill patients. *Design:* Pathophysiological study, prospective inclusions of 12 intubated adult patients. *Interventions:* Two PSV levels (high and low) and two expiratory trigger (ET) levels (high and low). *Measurements:* Surface electromyograms of the scalene, parasternal, and Alae Nasi muscles (peak, EMG_{max}; area under the curve, EMG_{AUC}); dyspnea visual analogue scale (VAS); prevalence of ineffective triggering efforts. *Main results:* For the three recorded muscles, EMG_{max} and EMG_{AUC} were significantly greater with low PS than high PS. The influence of ET was less important. A strong correlation was found between dyspnea and EMG_{max}. A significant inverse correlation was found between the prevalence of ineffective efforts and both dyspnea-VAS and EMG_{min}. *Conclusions:* Surface electromyograms of extradiaphragmatic inspiratory muscles provides a simple, reliable and non-invasive indicator of respiratory muscle loading/unloading in mechanically ventilated patients. Because this EMG activity is strongly correlated to the intensity of dyspnea, it could be used as a surrogate of respiratory sensations in mechanically ventilated patients, and might, therefore, provide a monitoring tool in patients in whom detection and quantification of dyspnea is complex if not impossible.

Keywords Mechanical ventilation · Patient–ventilator interaction · Electromyogram · Positive pressure support · Inspiratory muscles

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Introduction

There is growing evidence that dyspnea or respiratory discomfort is a critical issue in mechanically ventilated patients. Indeed, up to half of them experience a substantial level of dyspnea [1], which is associated with negative clinical outcomes [1]. Inappropriate ventilator settings, most often leading to "under assistance", are among the main determinants of dyspnea under mechanical ventilation [1, 2]. In such circumstances, dyspnea can be alleviated by increasing tidal volume (VT), but with the risk of "over assistance" that can be also be deleterious. Indeed, over assistance can induce dynamic hyperinflation and patient–ventilator asynchronies [3, 4], also associated with negative outcomes [4]. This justifies the search for monitoring tools that could help tailor ventilatory assistance to the demand of the patient without exceeding it (Fig. 1).

The electromyographic activity (EMG) of the extradiaphragmatic inspiratory muscles relates to the inspiratory drive to breathe [12, 13] and to respiratory sensations. It is therefore a logical monitoring target in the perspective of dynamically adapting ventilatory assistance. Surface EMGs of these muscles can be recorded in a routine ICU setting [5], but their value as surrogate biomarkers of dyspnea and their responsiveness to ventilator settings have seemingly not been studied in intubated, mechanically ventilated ICU patients.

In the present study, we hypothesised that the inspiratory electromyographic activity (iEMG) of three extradiaphragmatic inspiratory muscles (Alae nasi, scalenes, and parasternal intercostal) would vary with the level of ventilatory support administered to ICU patients and be related to the intensity of dyspnea if present. Additionally, we also studied the relationship between surface iEMGs, dyspnea, and the prevalence of ineffective inspiratory triggering efforts (a type of patient–ventilator asynchrony that is characteristic of over assistance).

Patients and methods

The study was conducted in a 16-bed ICU within a 1,600-bed university hospital. It was externally approved with regard to ethics and compliance to the French law on biomedical research (*"Comité de protection des personnes—Ile de France VI).* Informed consent was obtained from the patients.

Patients

Intubated or tracheostomized patients were eligible for inclusion in the study if: (1) they had been mechanically ventilated with inspiratory pressure support (IPS) for at least 12 h; (2) they had received no sedative, vasopressor or inotropic medication during the last 12 h; (3) their Ramsay score was ≤ 3 [6]; (4) according to the validated ATICE scale [7] they were awake and able to obey five commands ("open/close your eyes," "look at me," "open your mouth and put out your tongue," "nod your head," and "raise your eyebrows when I have counted up to five"). Patients were not included in the study when communication was likely to be difficult (auditory or visual impairment, insufficient command of French), when they were known to suffer from prior psychiatric or neurological disease, or when they presented with obvious delirium at the time of evaluation.

The study pertains to a convenience sample of twelve patients (Table 1).

Study protocol

The patients were ventilated using a Servo-i ventilator (Maquet Critical Care, Solna, Sweden). Positive end expiratory pressure (PEEP) was set at 4 cmH_2O and the fractional concentration of oxygen (FiO_2) was set to achieve a SpO_2 of 92 to 96 %. Two levels of pressure support (PS) were sequentially applied in random order. A low PS level (Low PS) targeted a VT of 6–8 ml/kg whereas a high PS level (High PS) targeted a VT of 8–12 ml/kg. Two expiratory trigger (ET) levels were also sequentially applied in random order: a high ET level (High ET) set at 30 % of the peak inspiratory flow [50 % in chronic obstructive pulmonary disease (COPD) patients] and a low ET level (Low ET) set at 5 % of the peak inspiratory flow (30 % in COPD patients). Four distinct conditions were thus defined (High PS–Low ET, Low PS–Low ET, High PS–High ET and Low PS–High ET).

Measurements

Flow and pressure

Flow was measured with a heated Fleisch pneumotachograph (Hans Rudolph, Kansas City, MO, USA) and airway pressure was measured by a pressure transducer (DP 15–32, Validyne, Northridge, CA, USA).

Electromyography

The EMG signals were collected using surface electrodes (Kendall, Tyco Healthcare, Germany). Bilateral parasternal intercostal-target recordings were obtained from the second intercostal space, close to the sternum (Fig. 2). Bilateral scalene-targeted recordings were

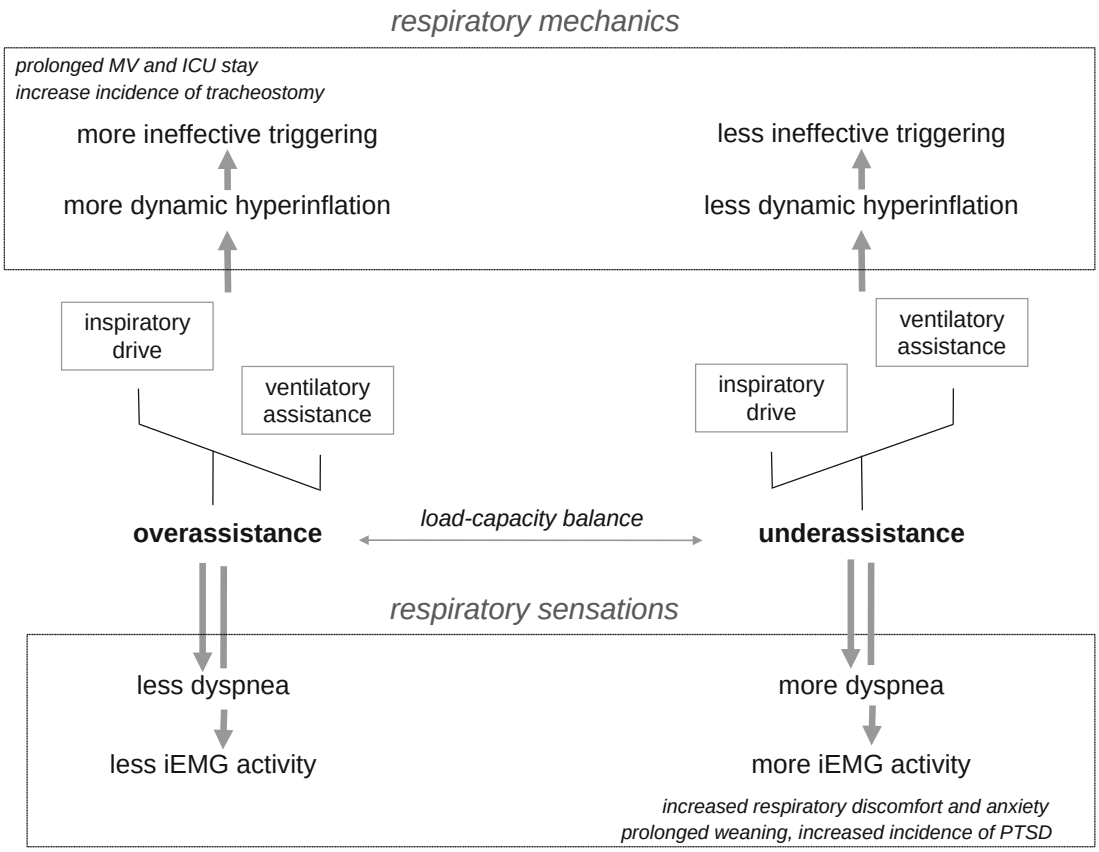

Fig. 1 Theoretical framework for the determinants of dyspnea, ineffective triggering and inspiratory electromyographic activity of extra diaphragmatic muscles (iEMG) in pressure support ventilation. *MV* mechanical ventilation, *PTSD* post traumatic stress disorders

obtained in the posterior triangle of the neck at the level of the cricoid cartilage. Alae nasi-targeted recordings were obtained by placing one electrode on each nostril (Fig. 2).

Dyspnea and comfort

At the end of each study period, dyspnea was rated using a visual analog scale (VAS) [8–10], and respiratory comfort was evaluated using the Adaptation to the Intensive Care Environment scale (ATICE) [7].

Data analysis

EMG signals were averaged according to Hug et al. [11] (see Figure E1 in the ESM). This produced a mean iEMG-RMS signal that was used to measure the maximum iEMG activity (EMG_{max}) and the iEMG area under the curve (EMG_{AUC}), expressed as the percentages of their maximum value. The ratio of EMG_{AUC} to VT was calculated as an index of neuro-mechanical coupling (EMG_{AUC}/VT).

Ineffective efforts were defined as an abrupt airway pressure drop ($\geq$0.5 cmH_2O) simultaneous to a flow decrease (in absolute value) and a concomitant EMG activity on extra diaphragmatic signals not followed by an assisted cycle during the expiratory period [11, 12].

Statistical analysis

The statistical analysis was performed using the Prism 4.01 software (GraphPad Software, San Diego, CA). Normality testing (Kolmogorov–Smirnov) consistently failed: results are, therefore, expressed as median (25–75 interquartile range) and non-parametric statistical tests were used. A Friedman analysis of variance was performed to compare the four ventilatory assistance conditions in terms of EMG_{max}, EMG_{AUC} and EMG_{min}, followed, when appropriate, by a pairwise comparison

Table 1 Description of the patients and ventilator settings

Patient	Gender (M/F)	Age (years)	BMI ($kg.m^{-2}$)	Cause of acute respiratory failure	Duration of MV at inclusion (d)	Total duration of MV (d)	High-PS (cmH_2O)	Low-PS (cmH_2O)	High-ET (%)	Low-ET (%)
1	M	84	26.3	AE-COPD	2	30	20	8	50	30
2	M	58	34.3	AE-COPD	3	8	20	10	50	30
3	M	60	23.3	AE-COPD	2	3	20	13	50	30
4	M	81	22.2	AE-COPD	2	4	16	8	50	30
5	M	39	15.2	Cardiogenic PO	2	16	17	10	30	5
6	F	38	28.6	Pneumonia, ALI	3	5	30	14	30	5
7	F	60	21.8	Cardiogenic PO	3	4	16	8	30	5
8	M	66	24.1	Pneumonia, ALI	4	4	16	10	30	5
9	M	60	22.0	AE-COPD	3	13	20	10	50	30
10	M	45	21.3	Septic shock, ALI	4	3	20	8	30	5
11	M	66	24.4	Pneumonia, ALI	7	7	22	12	30	5
12	F	58	36.1	Septic shock, ALI	6	5	20	9	30	5

Patient #5 and #9 died during their ICU stay

M male, *F* female, *BMI* body mass index, *AE-COPD* acute exacerbation on chronic obstructive pulmonary disease, *CPE* cardiogenic pulmonary oedema, *ALI* acute lung injury, *d* days, *MV* mechanical ventilation at inclusion, *High PS* high pressure support level targeting a tidal volume of 8–12 ml/kg. *Low PS* low pressure support level targeting a tidal volume of 6–8 ml/kg, *High-ET* high expiratory trigger level (30 % of the peak inspiratory flow, 50 % in COPD patients), *Low ET* low expiratory trigger level (5 % of the peak inspiratory flow, 30 % in COPD patients)

using Dunn's post hoc test. Comparison between the EMID of the three muscles were performed using a Kruskal–Wallis test. The relationship between dyspnea and iEMG values, VT or ineffective efforts, was examined using the Spearman's correlation. The normalisation/denormalisation technique described by Poon [13] was used to account for the use of within-patients replications in the correlation calculations. Differences were considered significant when the probability p of a type I error was below 5 %.

Results

Breathing pattern

Tidal volume was within the targeted ranges. Low PS VTs were significantly lower than High PS VTs ($p < 0.001$, Fig. 3, see also Table E1 in the ESM). Respiratory rates were generally higher under Low PS than under High PS, but the difference only reached statistical significance between Low PS–High ET and High PS–Low ET ($p < 0.05$, Fig. 3, see also Table E1 in the ESM). Similarly, SpO_2 was constant without PEEP or FiO_2 changes during the four conditions.

EMG activity

Parasternal intercostal and Alae Nasi EMGs were successfully recorded in all of the patients. A scalene EMG could not be recorded in 1 case (patient # 2). Overall, EMG_{max} and EMG_{AUC} tended to be greater under Low PS than under High PS, whichever the muscle considered (Fig. 4, see also Table E2 in the ESM). This difference was consistently significant between Low PS and High PS–Low ET). The impact of the ET level on EMG activity was less marked than the impact of the PS level: for a given level of PS (Low PS or High PS), changes in ET level did not have a significant impact on EMG_{max} nor EMG_{AUC}. The electromechanical inspiratory delay from iEMG onset to flow onset was significantly longer for the Alae Nasi [0.40 (0.20–0.61) s] than for the scalene and the parasternal intercostals [0.22 (0.00–0.31) and 0.21 (0.05–0.30) s, respectively; $p < 0.0001$]. They were not affected by ventilator settings.

Neuro-mechanical coupling

In line with the above, scalene EMG_{AUC}/VT and Alae Nasi EMG_{AUC}/VT were significantly lower under the High PS–Low ET condition than under the Low PS regimen ($p < 0.05$). Similarly, parasternal EMG_{AUC}/VT under High PS–Low ET was lower than under the Low PS–High ET condition [0.015 (0.000–0.049) and 0.198 (0.156–0.276), respectively; $p < 0.001$).

Ineffective triggering efforts

Ineffective triggering efforts were only observed in the five COPD patients (patients # 1 to # 4 and # 9). Their

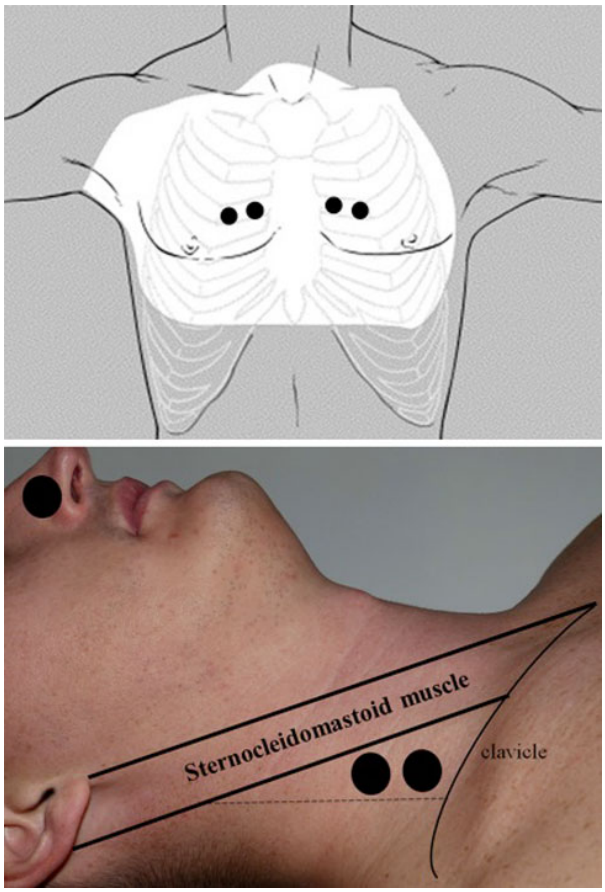

Fig. 2 Schematic representation of surface electrodes placement to record electromyographic activity (EMG) of parasternals (upper panel), scalene and Alae Nasi muscles (lower panel) Bilateral parasternal intercostal-target recordings were obtained from the second intercostal space, close to the sternum. Bilateral scalene-targeted recordings were obtained in the posterior triangle of the neck between the sternocleidomastoid muscle and the clavicle. The best side was retained for iEMG analyses. Alae nasi-targeted recordings were obtained by placing one electrode on each nostril

prevalence was higher with High PS [respectively, 1.8 (0.0–2.4) and 2.1 (1.8–2.2) min^{-1} with Low ET and High ET] than with Low PS conditions [respectively, 0.0 (0.0–0.3) and 0.0 (0.0–1.3) min^{-1} with Low ET and High ET; $p < 0.05$).

Dyspnea and comfort

Dyspnea ratings were significantly higher ($p < 0.001$) under Low PS, regardless of the ET level (Fig. 3). The ATICE score tended to be lower under Low PS than under High PS, but the difference reached statistical significance only between High PS–High ET and Low PS–High ET ($p < 0.001$).

Dyspnea ratings were negatively correlated with VT ($\rho = -0.45$, 95 % confidence interval (CI) 0.66 to −0.16, $p = 0.003$) and positively correlated with EMG_{max} [Alae nasi: $\rho = 0.90$ (0.81−0.95), $p < 0.0001$; scalene: $\rho = 0.96$ (0.91−0.98), $p < 0.0001$; parasternal intercostal: $\rho = 0.90$ (0.81−0.95), $p < 0.0001$] and EMG_{AUC} [Alae nasi: $\rho = 0.86$ (0.74−0.92), $p < 0.0001$; scalene: $\rho = 0.92$ (0.83–0.96), $p < 0.0001$; parasternal intercostal $\rho = 0.93$ (0.87−0.96), $p < 0.0001$]. Positive correlations were also found, expectedly, between dyspnea ratings and EMG_{AUC}/VT (Alae nasi: $\rho = 0.79$ (0.62−0.89); $p < 0.0001$; scalene: $\rho = 0.89$ (0.78−0.94); $p < 0.0001$; parasternal intercostal: $\rho = 0.89$ (0.80−0.94); $p < 0.0001$). Of note, an inverse correlation was found between dyspnea and ineffective triggering efforts [$\rho = -0.85$, (−0.96 to −0.50), $p < 0.001$]. The ATICE score was positively correlated with the tidal volume score [$\rho = 0.79$ (0.63−0.88), $p < 0.0001$].

Discussion

This study shows that the EMG activity of extra diaphragmatic inspiratory muscle responds to loading/unloading in acutely ill, mechanically ventilated patients. The study also evidences a strong relationship between the activity of these muscles and the intensity of dyspnea.

Inspiratory EMGs and ventilatory support

We used an inspiratory phase-locked EMG analysis technique to optimise inspiratory neck muscles surface recordings [11] and to study the responsiveness of extra diaphragmatic inspiratory muscles to inspiratory loading/unloading. In ICU patients, increased inspiratory neck muscles activity has been associated with insufficient levels of IPS during ventilator weaning [14], ventilator trigger asynchrony [15], and weaning failure [16]. Recent data indicate that the EMG activity of the parasternal intercostals, closely related to inspiratory drive, could provide a clinically useful biomarker in evaluating treatment response during acute exacerbations of COPD [17]. In this context, our study extends the current knowledge by showing that both an upper airway dilator (Alae nasi), and neck and rib cage inspiratory muscles similarly respond to the level of ventilatory support provided to mechanically ventilated ICU patients.

Of note, this study is seemingly the first to document a load-related activity of the Alae nasi in adult patients placed under mechanical ventilation. This is of importance, given the easy accessibility of this muscle for monitoring purposes and the easiness to obtain cross-talk free quality recordings. In our patients, Alae nasi was

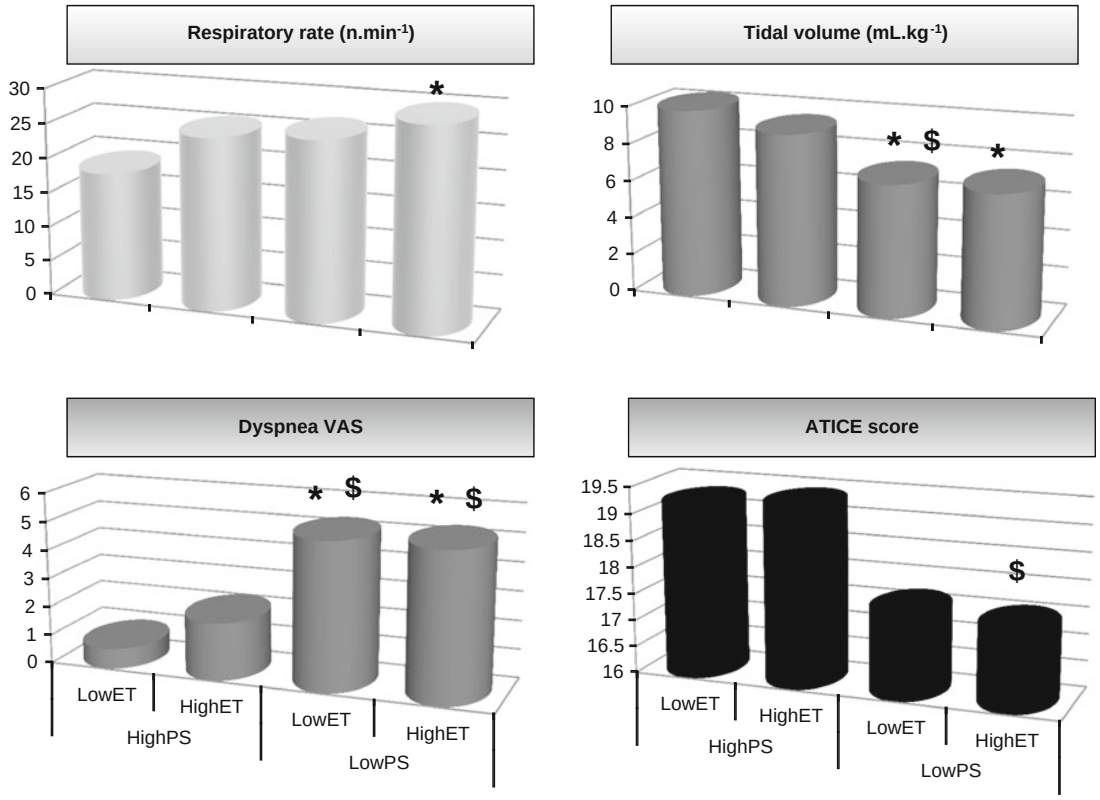

Fig. 3 Respiratory rate, tidal volume, dyspnea intensity as assessed with the visual analogic scale (VAS) and adaptation to the Intensive Care Environment scale (ATICE) *High PS* high pressure support level targeting a tidal volume of 8–12 ml/kg, *Low PS* low pressure support level targeting a tidal volume of 6–8 ml/kg, *High-ET* high expiratory trigger level (30 % of the peak inspiratory flow, 50 % in COPD patients); *Low ET* low expiratory trigger level (5 % of the peak inspiratory flow, 30 % in COPD patients). *Columns* are median and *bars* are interquartile range. * $p < 0.05$ with Low PS–High ET; $^{\$}p < 0.05$ with Low PS–Low ET

activated significantly before the scalenes and the parasternal intercostals, as physiologically expected [18], and in spite of the upper airway being bypassed by the endotracheal prosthesis.

Dyspnea and inspiratory EMG

In our patients, the intensity of dyspnea was closely correlated with the various EMG indices of extra diaphragmatic inspiratory muscles activity. Two particular features warrant emphasis. Firstly, the dyspnea-EMG relationships were particularly strong in our patients, with circa two-thirds of the variance of dyspnea being explained by EMG values. This relationship is far stronger than that which has previously been described in normal subjects with exactly the same methodology [19]. One possible explanation for this observation could be the tightness of the neuro-mechanical coupling in ICU patients as compared to normal individuals [20].

Secondly, in those of our patients diagnosed with COPD, dyspnea was the less intense under the highest levels of assistance (Fig. 3). Yet this corresponded to the highest prevalence of patient–ventilator asynchronies of the "ineffective triggering effort" type (inclusive of, in line with a simple cross correlation phenomenon, an inverse relationship between dyspnea and the prevalence of ineffective efforts). This situation is characteristic of dynamic hyperinflation [4, 15, 21]. Lower levels of ventilatory support in our patients dramatically decreased the prevalence of ineffective efforts, but were accompanied by an increase of the intensity of dyspnea and EMG activity. This is a typical example of "Gordian knot" situations where a ventilatory management strategy that is aimed at reducing morbidity exposes the patients to dyspnogenic stimuli. Indeed, patient–ventilator asynchronies are associated with negative clinical outcomes such as an increased duration of an ICU stay and a more frequent recourse to tracheostomy [4]. Intensivists are generally keen to avoid them. However, fighting

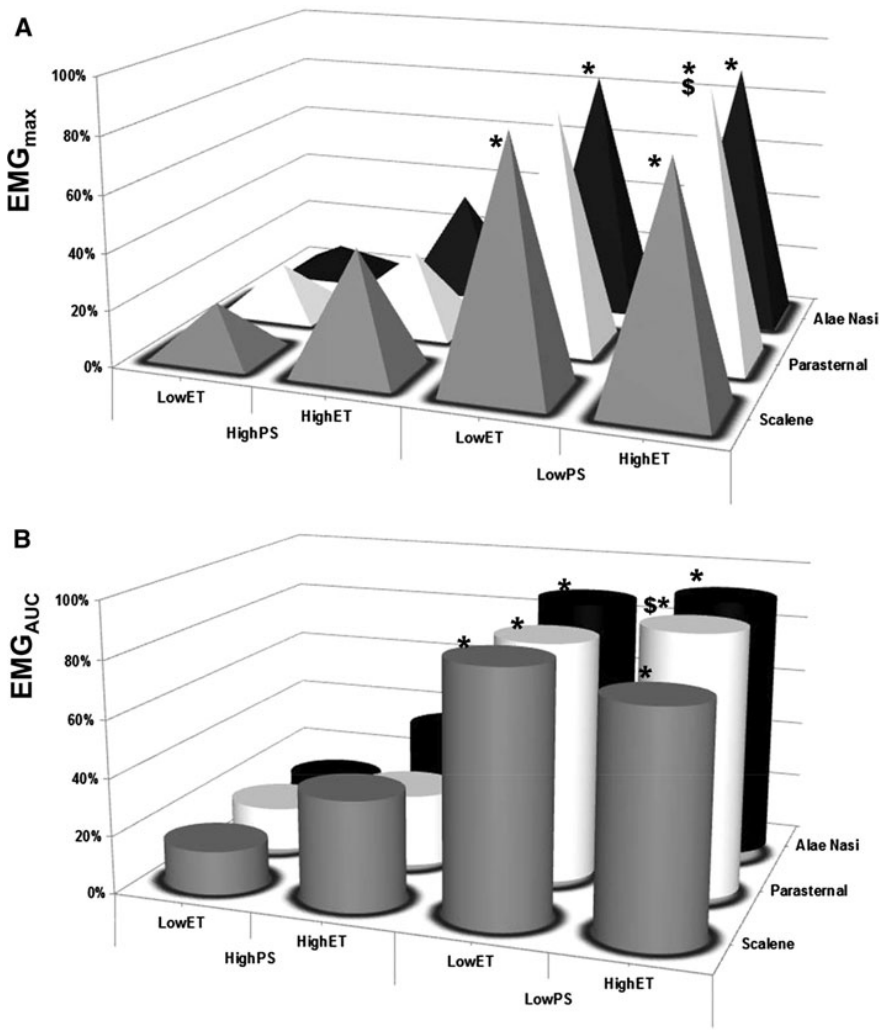

Fig. 4 Electromyographic (EMG) activity of scalene, intercostal parasternal and Alae nasi muscles Peak of the averaged electromyographic activity (EMG_{max}, Panel A) and area under the averaged EMG activity (EMG_{AUC}, Panel B). EMG_{max} and EMG_{AUC} are expressed as a proportion of the maximum value. *High PS* high pressure support level targeting a tidal volume of 8–12 ml/kg; *Low PS* low pressure support level targeting a tidal volume of 6–8 ml/kg; *High-ET*, high expiratory trigger level (30 % of the peak inspiratory flow, 50 % in COPD patients); *Low ET* low expiratory trigger level (5 % of the peak inspiratory flow, 30 % in COPD patients). *Columns* are median. * $p < 0.05$ with Low PS–High ET; $^{\$}p < 0.05$ with Low PS–Low ET

ineffective triggering asynchronies by reducing the level of assistance induces dyspnea. Yet dyspnea is a noxious sensation [22] that should absolutely be avoided, mostly for obvious reasons of comfort, but also because of its possible association with negative clinical outcomes [1]. This concern could become increasingly prominent with the generalization of low tidal volume ventilation strategies beyond ARDS [23, 24].

Study limitations

Our population is a convenience sample of limited size. Although we were able to evidence statistically significant results, this sets an obvious limit to our results regarding generalisability. Our results, however, extend to actual ICU patients the proof of concept data already available in normal subjects [19]. Also, we studied surface EMGs (as opposed to needle EMGs) for the sake of simplicity, comfort and safety. Except for the alae nasi, this implies that we cannot be entirely be precise regarding the muscles sampled because of cross-talk issues. This should, however, not change the messages very much. Finally, we did not perform any measure of diaphragm function, which prevents us from providing a full description of respiratory muscle recruitment in our patients. This was not the purpose of the study; rather, it was designed with practical applications in mind. In addition, there are reasons to think that even if an increased diaphragm activity is related to breathlessness in certain situations, diaphragm activity may not be the most pertinent index to monitor in situations of acute inspiratory loading [25] where extra diaphragmatic inspiratory muscles become the prominent actors of the act of breathing.

Conclusions and perspective

In a recent study, 47 % of patients receiving mechanical ventilation reported being dyspneic on the first day when they were able to answer questions from the investigator. This is a very high figure, all the more so that the median rating of the dyspneic sensation on a visual analogue scale was slightly above 5. In 35 % of these patients, dyspnea receded after elementary ventilator settings adjustments [1], or, in other words, after improving the load-capacity balance of the system through external unloading. Dyspnea was also associated with anxiety and a longer duration of the ICU stay. These observations, beyond mere common sense, emphasize the importance of detecting and monitoring dyspnea in the ICU, with the aim of alleviating it. Particularly (but not solely) in patients with an impaired verbal communication, surrogates to words are needed. We submit that the results of the present study justify further efforts to validate surface EMGs of extra diaphragmatic inspiratory muscles as such surrogates. They would have the advantage of providing continuous monitoring to alert caregivers about putative dyspnea and prompt dyspnea targeted evaluations that would start, whenever possible, by asking the patient about his or her respiratory sensations. They would also help to titrate ventilatory assistance to patients' needs. This titration could be achieved by analyzing extra diaphragmatic inspiratory muscle EMG as a surrogate biomarker of dyspnea and an indicator of probable under assistance on one hand, and by identifying ineffective triggering (from pressure and flow signals) as a marker of over assistance on the other hand. Practically, a reduction of the EMG activity of extra diaphragmatic inspiratory muscles after increasing the level of ventilator assistance with no or few ineffective triggering might suggest that ventilator support is well-tailored.

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Conflicts of interest In 2009 and 2010, the *Association pour le Développement et l'Organisation de la Recherche en Pneumologie et sur le Sommeil (ADOREPS)* received an unrestricted research grant from Maquet France SA, Orléans, France, to support pathophysiological research studies on the "neurally adjusted ventilatory assist" (NAVA) mode.

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Dyspnea and surface inspiratory electromyograms in mechanically ventilated patients

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Mathieu Raux ; Francois Hug ;Thomas Similowski ; Alexandre Demoule

Electronic Supplement Material

Extended Methods

Patients and methods

The study was conducted in a 16-bed ICU within a 1600-bed university hospital. It was externally approved with regard to ethics and compliance to the French law on biomedical research (*"Comité de protection des personnes – Ile de France VI").* Informed consent was obtained from the patients.

Patients. Intubated or tracheostomised patients were eligible for inclusion in the study if: 1) they had been mechanically ventilated with inspiratory pressure support (IPS) for at least 12 hours; 2) they had received no sedative, vasopressor or inotropic medication during the last 12 hours; 3) their Ramsay score was ≤ 3 [1]. 4) according to the validated ATICE scale [2] they were awake and able to obey to five commands ("open/close your eyes", "look at me", "open your mouth and put out your tongue", "nod", and "raise your eyebrows when I have counted up to five"). Patients were not included in the study when communication was likely to be difficult (auditory or visual impairment, insufficient command of French), when they were known to suffer from prior psychiatric or neurological disease, or when they presented with obvious delirium at the time of evaluation.

The study pertains to a convenience sample of twelve patients (Table 1).

Study protocol. The patients were studied lying at 30° with their head maintained in the neutral position. They were ventilated using a Servo-i ventilator (Maquet Critical Care, Solna, Sweden), with a high sensitivity flow trigger ($1L.min^{-1}$) and a 100ms inspiratory slope. Positive end expiratory pressure (PEEP) was set at 4 cmH_2O and the fractional concentration of oxygen (FiO_2) was set to achieve a SpO_2 of 92% to 96%. For all patients, the PEEP and FiO_2 were kept constant throughout the four experimental conditions. Two levels of pressure support (PS) were sequentially applied in random order. A low PS level (LowPS) targeted a tidal volume of 6-8 ml/kg whereas a high PS level (HighPS) targeted a tidal volume of 8-12

ml/kg. Two expiratory trigger (ET) levels were also sequentially applied in random order: a high ET level (HighET) set at 30% of the peak inspiratory flow (50% in chronic obstructive pulmonary disease [COPD] patients) and a low ET level (LowET) set at 5% of the peak inspiratory flow (30% in COPD patients). Four distinct conditions were thus defined (HighPS-LowET, LowPS-LowET, HighPS-HighET and LowPS-HighET), and applied during four 20 minutes periods. The subsequent results pertain to the analysis of the last 10 minutes of each of these epochs.

Measurements.

Flow and pressure. Flow was measured with a heated Fleisch pneumotachograph (Hans Rudolph, Kansas City, MO, USA) placed between the endotracheal tube and the Y-piece of the ventilator circuit. Airway pressure was measured proximal to the endotracheal tube by a pressure transducer (DP 15-32, Validyne, Northridge, CA, USA).

Electromyography. The EMG signals were collected using surface electrodes (48 x 33mm, ref 31.1925.21, Kendall, Tyco Healthcare, Germany). Bilateral parasternal intercostal-target recordings were obtained from the second intercostal space, close to the sternum (see Fig E1 in the ESM). Bilateral scalene-targeted recordings were obtained in the posterior triangle of the neck at the level of the cricoid cartilage. The best side was retained for iEMG analyses. *Alae nasi*-targeted recordings were obtained by placing one electrode on each nostril (see Fig E2 in the ESM). The signals were first pre-amplified (gain of 0.5) and pre-filtered below 10Hz and above 1,000 Hz (Electronique du Mazet, Le Mazet Saint Voy, France).

EMG, flow and pressure were sampled at 2,000 Hz (PowerLab, AD Instrument, Hastings, UK) and stored on file for subsequent analysis.

Dyspnea and comfort. At the end of each study period, dyspnea was rated using a visual analog scale (VAS) [3-5], and respiratory comfort was evaluated using the Adaptation to the Intensive Care Environment scale (ATICE) [2].

EMG processing and data analysis. EMG signals were averaged according to Hug et al. [6] (Figure E1). In brief; inspiratory efforts were identified from the flow signal. The EMG signal was then truncated in as many epochs as there were inspiratory efforts, each epoch starting 1s before the beginning of the corresponding inspiratory efforts and ceasing 2s after its conclusion so as to contain the full inspiratory-related EMG activity. In the end, eighty consecutive iEMG epochs phase-locked to inspiration were root mean-squared (RMS) and ensemble-averaged. This produced a mean iEMG-RMS signal that was used to measure; 1) the electromechanical inspiratory delay (EMID) from iEMG onset to flow onset; 2) the maximum iEMG activity (EMG_{max}); 3) the iEMG area under the curve (EMG_{AUC}). EMG_{max} and EMG_{AUC} were expressed as the percentages of their maximum value as observed in any of the four conditions. The ratio of EMG_{AUC} to tidal volume (V_T) was calculated as an index of neuro-mechanical coupling (EMG_{AUC}/ V_T).

Ineffective efforts were defined as an abrupt airway pressure drop ($\geq$ 0.5 cmH_2O) simultaneous to a flow decrease (in absolute value) and not followed by an assisted cycle during the expiratory period [6, 7]. In case of a doubt on an artefactual variation of pressure and flow, the presence of a concomitant EMG activity on extra diaphragmatic signals recordings ascertained the reality of the ineffective triggering.

Statistical Analysis. The statistical analysis was performed using the Prism 4.01 software (GraphPad Software, San Diego, CA). Normality testing (Kolmogorov-Smirnov) consistently failed: results are therefore expressed as median [25-75 interquartile range] and non-parametric statistical tests were used. A Friedman analysis of variance was performed to compare the 4 ventilatory assistance conditions in terms of EMG_{max} , EMG_{AUC} and EMG_{min}, followed, when appropriate, by a pairwise comparison using Dunn's post-hoc test. Comparison between the EMID of the 3 muscles were performed using a Kruskal-Wallis test. The relationship between dyspnea and iEMG values, tidal volume or ineffective efforts, was

examined using the Spearman's correlation. The normalisation/denormalisation technique described by Poon [8] was used to account for the use of within-patients replications in the correlation calculations. Differences were considered significant when the probability p of a type I error was below 5%.

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Tables

Table E1. Respiratory rate, tidal volume, dyspnea intensity as assessed with the visual analogic scale (VAS) and adaptation to the Intensive Care Environment scale (ATICE).

	HighPS		**LowPS**	
	LowET	**HighET**	**LowET**	**HighET**
Tidal volume (mL.kg^{-1})	10.5 [8.1-11.7]	8.8 [8.1-11.5]	6.8 [6.2-7.5] *$	6.9 [6.1-7.9]*
Respiratory rate (breaths.min^{-1})	20 [13-22]	23 [20-29]	24 [19-31]	27 [24-34]*
Minute ventilation (L.min^{-1})	12.1 [7.3-14.0]	12.5 [10.0-13.9]	12.3 [11.1-14.2]	12.1 [8.3-12.9]
Dyspnea intensity (VAS, from zero to 10)	0.0 [0.0-1.5]	1.0 [0.0-4.0]	5.0 [3.5-7.0]*$	4.0 [3.5-7.0]*$
ATICE scale	19.0 [18.5-20.0]	20.0 [19.5-20.0]	18.0 [16.5-18.5]	18.0 [15.5-19.0]$

HighPS, high pressure support level targeting a tidal volume of 8-12 ml/kg; *LowPS*, low pressure support level targeting a tidal volume of 6-8 ml/kg; *High-ET*, high expiratory trigger level (30% of the peak inspiratory flow, 50% in COPD patients); *LowET*, low expiratory trigger level (5% of the peak inspiratory flow, 30% in COPD patients).

Columns are median and bars are interquartile range.

* $p < 0.05$ with LowPS-High-ET; $ $p<0.05$ with LowPS-LowET.

Table E2. Electromyographic (EMG) activity of the scalenes, intercostal parasternal, and *Alae nasi* muscles.

	Scalenes				**Parasternal intercostals**				***Alae nasi***			
	HighPS		LowPS		HighPS		LowPS		HighPS		LowPS	
	LowET	HighET	LowET	HighET	LowET	HighET	LowET	HighET	LowET	HighET	LowET	HighET
EMG_{max} (%)	12 [0-33]	51 [0-80]	88 [80-99] *	100 [77-100] *	16 [0-34]	20 [0-60]	82 [78-89]	100 [100-100] *$	10 [8-11]	27 [7-56]	81 [76-96]*	100 [78-100]
EMG_{AUC} (%)	11 [0-33]	41 [0-67]	83 [78-99] *	100 [63-100] *	11 [0-33]	22 [0-50]	81 [76-96] *	100 [76-96] *$	11 [5-16]	35 [8-50]	82 [80-100]*	100 [78-100]
EMG_{min} (%)	9 [0-32]	43 [0-87]	81 [72-85]*	100 [74-100]*	10 [0-29]	26 [0-59]	80 [60-96]	100 [86-100]*$	12 [1-20]	33 [8-62]	82 [73-100]*	100 [80-100]*

HighPS, high pressure support level targeting a tidal volume of 8-12 ml/kg; *LowPS*, low pressure support level targeting a tidal volume of 6-8 ml/kg; *High-ET*, high expiratory trigger level (30% of the peak inspiratory flow, 50% in COPD patients); *LowET*, low expiratory trigger level (5% of the peak inspiratory flow, 30% in COPD patients); EMG_{max}, peak of electromyographic activity; EMG_{AUC}, area under the EMG curve; EMG_{min}, EMG activity per minute calculated as EMG_{AUC} x (respiratory rate + ineffective effort per minute).

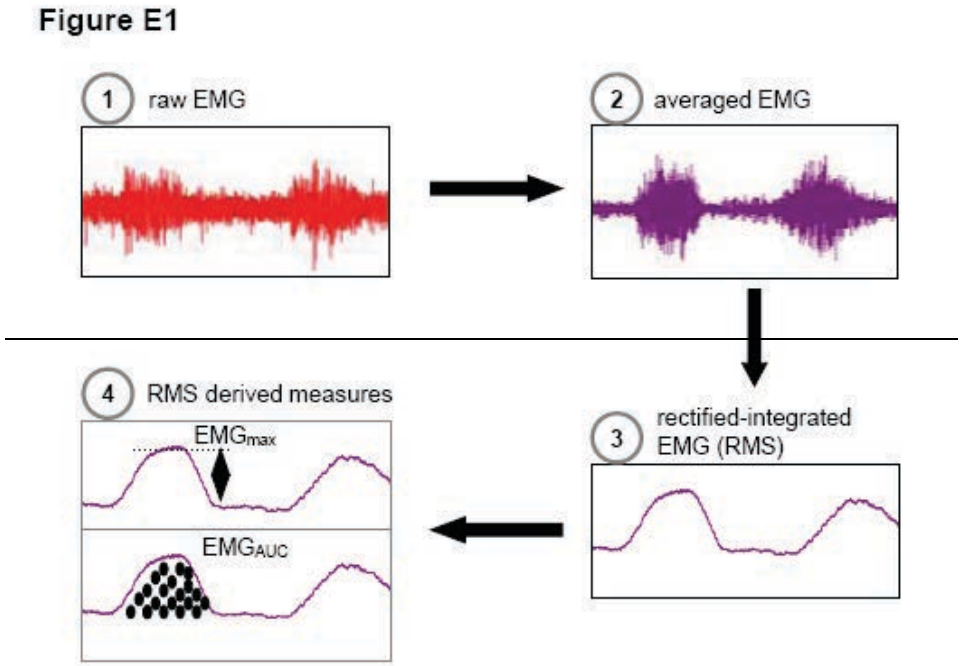
EMG_{max}, EMG_{AUC} and EMG_{min} were expressed as for each patient as a proportion of the maximum value measured in any the four conditions.

Data are median [interquartile range]. * $p < 0.05$ with HighPS-LowET; $ $p<0.05$ with HighPS-HighET

Figures

Figure E1. Principle of the electromyographic signal analysis (EMG)

$EMG_{average}$, averaged electromyographic signal (6); *RMS*, average signal root-mean-square; EMG_{max} , peak of the EMG activity; EMG_{AUC}, area under the curve of the EMG signal.



Conclusions et perspectives

L'étude de la dysharmonie patient-ventilateur est complexe. Elle associe l'étude d'éléments objectifs (asynchronie patient ventilateur, proportionnalité de l'assistance, variabilité du profil ventilatoire, complexité et index de couplage neuro-mécanique) avec l'étude des sensations subjectives qui peuvent y être associées (dyspnée, anxiété…).

Les modes ventilatoires disponibles en réanimation se sont récemment enrichis de modes proportionnels. La PAV et le NAVA en sont les deux principaux représentants. Si des travaux antérieurs sur la PAV avaient déjà suggéré une meilleure harmonie patient-ventilateur en ventilation invasive et en VNI, tel n'était pas le cas en NAVA. Ainsi, les données exposées au chapitre 1 ont été parmi les premières à mettre en évidence une justification physiologique à la meilleure harmonie patient-ventilateur observée en NAVA. Au travers de l'étude de la variabilité et de la complexité, la NAVA semblait donc améliorer l'adéquation charge-capacité ou le couplage neuro-mécanique. Ce mode pourrait révéler et permettre « l'expression » de la variabilité et de la complexité de la commande centrale du patient. Cette notion est de notre point de vue importante car il existe une relation entre cette variabilité du profil ventilatoire et le pronostic de patients ventilés en réanimation. Par exemple, dans le sevrage ventilatoire, l'analyse de la variabilité des descripteurs du comportement ventilatoire au cours de l'épreuve de ventilation spontanée réalisée pour les besoins du sevrage était la plus performante pour prédire le succès du dit sevrage (95). Au-delà du sevrage de la ventilation mécanique, de très récentes données suggèrent que la variabilité ventilatoire pourrait être un facteur pronostique de mortalité en réanimation (177). Ainsi, un nouveau mode ventilatoire, dénommé «noisy ventilation® », qui intègre la

variabilité dans son algorithme avec pour objectif de délivrer un volume courant variable (174) est actuellement développé (178). Les résultats prometteurs des modes proportionnels exposés dans les chapitre 1, 2, 3 et la «noisy ventilation® », tous associés à un niveau de variabilité supérieur à celle des modes plus conventionnels nous montrent que la variabilité pourrait devenir un outil thérapeutique en ventilation mécanique. De même en VNI, les modes proportionnels pourrait eux aussi améliorer l'harmonie patient ventilateur (124-126, 179, 180). A titre d'exemple, les données exposées au chapitre 2 suggèrent que l'utilisation du mode NAVA en VNI, lui même responsable de fuites générées par la sonde naso-gastrique, pourrait permettre une réduction des asynchronies patient-ventilateur liées aux fuites. Les fuites sont un problème majeur en VNI et réduire les asynchronies patient-ventilateur est crucial car elles sont sources de mauvaise tolérance de la technique (7), ce qui augmente le risque d'échec (30, 31). Une perspective intéressante pour s'affranchir des limites de la NAVA pourrait être de développer un mode ventilatoire asservie à l'activité musculaire des muscles extra-diaphragmatiques.

L'étude des sensations associées à la dysharmonie patient-ventilateur est elle aussi complexe. A titre d'exemple l'étude de la dyspnée est subjective, multifactorielle et d'analyse difficile en ventilation mécanique. De plus, l'intérêt porté à la dyspnée en ventilation mécanique est récent et limité à quelques travaux (5, 30) (voir infra, annexe 1). Attirer l'attention des cliniciens sur l'importance majeure de minimiser la dyspnée et l'inconfort respiratoire chez les patients faisant l'objet d'une assistance ventilatoire mécanique est néanmoins nécessaire. En effet, au-delà de la souffrance immédiate que représente la dyspnée, il est vraisemblable qu'elle soit associée à des effets délétères au regard des principaux critères cliniques d'évaluation de la réanimation (morbi-mortalité, durée de ventilation, durée de séjour). De plus, le syndrome de stress post-traumatique (PTSD) est aujourd'hui une séquelle bien établie des séjours en réanimation (181). Ses facteurs de

risques sont les divers facteurs anxiogènes associés à un séjour en réanimation (73, 182, 183), et notamment l'assistance ventilatoire (183-186). Ainsi, les scores quantifiant les symptômes évocateurs de PTSD sont clairement corrélés aux souvenirs de détresse respiratoire et à la durée de ventilation mécanique (181). Il est dés lors très probable que la dyspnée soit l'un des évènements traumatique participant à la genèse d'un PTSD. L'étude multicentrique DYSTRESS (impact de la DYspnée sous assistance ventilatoire sur le pronostic et syndrome de STRESS post-traumatique) permettra prochainement de mieux identifier la prévalence de la dyspnée en ventilation mécanique et ses conséquence à court et moyen terme.

Toutes ces données précédemment exposées plaident pour une surveillance régulière de la dyspnée en réanimation. En revanche, surveiller la dyspnée dans ce contexte n'est pas facile. En effet, outre les difficultés associées à l'évaluation d'un symptôme —subjectif par nature—, les multiples stimulus auxquels sont exposés les patients de réanimation placés sous assistance ventilatoire mécanique (modification de la sédation, de l'analgésie, mobilisation, effort, complications intercurrente…) implique que la sensation dyspnéique est par nature labile et susceptible de connaître de nombreuses variations sur des intervalles de temps brefs. L'identification d'outils de détection de la dyspnée était l'un de nos objectifs. Nos données exposées dans le chapitre 4 offrent des éléments de réponse. En effet, le monitorage d'index EMG pourrait ainsi servir de signal d'alarme, une augmentation de l'activité de muscles comme les scalènes, les parasternaux intercostaux, ou *Alae nasi* —tous facilement accessible à l'enregistrement— incitant le clinicien à chercher une cause à cette dyspnée. L'étude de l'harmonie patient-ventilateur en réanimation est récente et certaines situations spécifiques de réanimation n'ont pas encore fait l'objet de travaux. A titre d'exemple, l'utilisation d'une extracoporeal membrane oxygénation (ECMO) permet de modifier artificiellement la PaO_2 et la $PaCO_2$ sans modifier les réglages du ventilateur. Ainsi, l'étude de la dyspnée dans cette situation unique pourrait être très pertinente. De même, les asynchronies patient-ventilateur

semblent être importantes chez ces patients ayant une faible compliance pulmonaire (187). L'utilisation du mode NAVA pourrait ainsi permettre de réduire le nombre d'asynchronie patient-ventilateur (187) et de maintenir une ventilation protectrice (188).

Enfin, il est important de conserver à l'esprit que nos travaux exposés dans cette thèse sont essentiellement physiologiques. Même s'il existe certains éléments indirects pouvant suggérer un bénéfice clinique d'améliorer l'harmonie patient-ventilateur et de réduire les sensations respiratoires associées, l'impact clinique et le bénéfice à long terme restent mal définis et peu étudiés. La finalité des travaux de recherche que nous présentons est de progresser vers une meilleure connaissance de la dysharmonie patient ventilateur. L'impact clinique de l'utilisation des modes proportionnels et d'une détection précoce de la dyspnée doit maintenant être évalué par des essais cliniques.

ANNEXE 1

Dyspnea in mechanically ventilated critically ill patients

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Objectives: **Ensuring the comfort of intensive care unit patients is crucial. Although control of pain has been extensively addressed in this setting, data on dyspnea in mechanically ventilated patients are scant. The objective of this study was to assess the prevalence of dyspnea in mechanically ventilated patients, identify its clinical correlates, and examine its impact on clinical outcomes.**

Design, Setting, and Participants: **At two medical intensive care unit sites, we conducted a prospective 6-month observational study of intubated or tracheotomized patients who were mechanically ventilated for >24 hrs. We enrolled 96 patients (age, 61 ± 18 yrs; Simplified Acute Physiology Score II 43 [interquartile range, 31–60]) as soon as they could answer symptom-related questions. Dyspnea was evaluated on a "yes–no" basis; if yes, it was followed by a visual analog scale and descriptor choice ("air hunger" and/or "respiratory effort"). Pain and anxiety were also assessed by visual analog scale.**

Measurements and Main Results: **Forty-five patients (47%) reported dyspnea (respiratory effort in seven cases, air hunger in 15, both in 16, and neither of these in seven). Dyspneic and nondyspneic patients did not differ in terms of age, Simplified Acute Physiology Score II, indication for mechanical ventilation, respiratory rate, clinical examination, chest radiograph, or blood gases. Dyspnea was significantly associated with anxiety (odd ratio [OR], 8.84; 95% confidence interval [CI], 3.26–24.0), assist-control ventilation (OR, 4.77; 95% CI, 1.60–4.3), and heart rate (OR, 1.33 per 10 beats/min; 95% CI, 1.02–1.75). Adjusting ventilator settings improved dyspnea in 35% of patients. Successful extubation within 3 days was significantly less frequent in patients whose dyspnea failed to recede after adjusting ventilator settings (five [17%] vs. 27 [40%]; $p = .034$).**

Conclusions: **Dyspnea is frequent, intense, and strongly associated with anxiety in mechanically ventilated patients. It can be sensitive to ventilator settings and seems to be associated with delayed extubation. (Crit Care Med 2011; 39:000–000)**

Key Words: ***mechanical ventilation, dyspnea, respiratory sensations, patient anxiety, breathing pattern***

Dyspnea is a tormenting sensation that is often prominent in patients with respiratory distress. An important objective of mechanical ventilation (MV) is to assuage this symptom. Dyspnea can, however persist, reappear, or reincrease after the institution of MV. This can reveal complications (like pneumothorax, pneumonia, cardiac failure, anemia, etc.) or inappropriate ventilator settings. Dyspnea could therefore be useful as a clinical management tool. It has, however, not been studied to any great extent in mechanically ventilated patients.

Beyong being a major source of physical discomfort (1), dyspnea shares many physiological and clinical features with pain (2–6). Like pain, it is intricated with anxiety (7, 8). This must make it a topmost preocuppation of intensive care unit (ICU) clinicians and nurses whose mission is to relieve symptoms in addition to treating disease processes. Of note, current ICU management trends designed to reduce iatrogenic complications and shorten ICU stays also carry the risk of exposing the patients to stronger dyspnogenic stimuli for longer periods. This is true for reduced sedation (9), reduced tidal volume (10), and the preservation of spontaneous ventilatory activity in patients with severely compromised lung function (11). Neglecting dyspnea in these circumstances is bound to cause suffering. It could also counterbalance physiological benefits in terms of clinical outcomes. It could also have a negative distant impact through negative recollections.

Nevertheless, dyspnea is not routinely assessed in ICU patients, except perhaps during weaning from MV (12, 13). A study by Connelly et al (14), in 21 patients receiving MV, found that dyspnea was common and correlated with the "vigor" component of a mood score. A study by Powers et al (15) found that nearly half of 28 mechanically ventilated patients reported moderate to severe dyspnea. Anxiety has been assessed in mechanically ventilated patients (16) but never concomitantly with dyspnea.

In this context, we conducted this prospective observational study in mechanically ventilated patients able to communicate to gain further insight into the prevalence, intensity, mechanisms, and prognostic value of dyspnea. We were particularly interested in its association with ventilator settings because this represents an easy target for intervention and with the relationships of dyspnea to anxiety and pain.

METHODS

Patients. The study population included consecutive mechanically ventilated adult

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medical patients admitted either to the ICU (16 beds) of Raymond Poincaré University Hospital (360 beds) or to the medical ICU (ten beds) of the department of respiratory and ICU at la Pitié-Salpétrière hospital (1800 beds) over 6 months. The protocol was approved by the legal and ethical body recognized by French law (Comité de Protection des Personnes, Saint Germain en Laye, France), which waived written informed consent.

Patients were eligible to participate in the study if they had been mechanically ventilated for >24 hrs—noninvasive ventilation excluded—awake, according to the validated Adaptation To the Intensive Care Environment (ATICE) scale (17), and able obey to five simple commands ("open/close your eyes," "look at me," "open your mouth and put out your tongue," "nod your head," and "raise your eyebrows when I have counted up to five"). They were included as soon as they fulfilled these conditions. Patients were not included in the study when communication was likely to be difficult (auditory or visual impairment, insufficient command of French) or when they were known to have prior psychiatric or cognitive disorders.

Study Procedure. During the study period, the patients at the two ICU sites were systematically screened for inclusion in the study on a daily basis, between 9 and 12 AM. Potential candidates were studied and enrolled as soon as they were sufficiently alert to answer the previously described five commands. They were only studied once during their ICU stay.

Assessment of Dyspnea, Anxiety, and Pain. Once enrolled, the patients were first asked "do you have trouble breathing"? If the answer was yes, then they were asked to rate the intensity by placing a cursor on a 10-cm visual analog scale (VAS) bounded on the left by "no respiratory discomfort" and on the right by "intolerable respiratory discomfort." The patients were then asked to choose "air hunger," "excessive respiratory effort," or both, to characterize their respiratory sensations. Finally, they were presented with two additional 10-cm VASs to evaluate anxiety ("no anxiety" to "intolerable anxiety") and pain ("no pain" to "intolerable pain"). When a patient understood the principle of assessment but was unable to move the VAS cursor him- or herself, the observer helped the patient by holding the scale and supporting the patient's forearm. If the subject was unable to move their arms (like in few cases with severe neuromuscular impairment), the observers were allowed to manipulate the VAS cursor following instructions given by the patient. However, this was not recommended and avoided whenever possible. The cursor was never adjusted directly or solely by the investigator.

Descriptive Variables. To describe the study population, we recorded age, gender, the severity of illness—Simplified Acute Physiology score II—the indication for MV, the nature of the patient–ventilator interface (orotracheal intubation or tracheotomy), and the duration of MV at the time of dyspnea assessment. To describe the patients at the time of assessment, we recorded heart rate, systolic and diastolic blood pressure, respiratory rate, and temperature. A detailed "respiratory-oriented" physical examination was performed, systematically noting the presence or absence of auscultatory abnormalities, the presence or absence of inspiratory neck muscle activity, an inspiratory retraction of the supraclavicular fossae or intercostal spaces, an abdominal paradox, or a phasic activation of upper airway dilators (genioglossus and alae nasi). These signs were grouped into a single variable, termed "abnormal breathing dynamics" (coded 0 when none of the signs were present and 1 when any of these were observed). Blood hemoglobin and arterial blood gases (PaO_2, $PaCO_2$) were recorded as well as chest radiograph abnormalities. Finally, we noted the type of tracheal tube and ventilator settings, including the ventilatory mode, minute ventilation, pressure support level, inspiratory flow, and positive end-expiratory pressure. The duration of MV and the occurrence of successful extubation within the 3 days after the assessment of dyspnea were gathered as well as the mortality rate and the ICU length of stay.

Role of Ventilator Settings. When a patient reported being dyspneic, the investigator immediately informed the physician in charge. If the physician chose to adjust the ventilator settings, he was asked to do so in a standardized and stepwise manner, including a reevaluation of the patient's perceptions after each change. No further setting alterations were made after a given change had been associated with a decrease in dyspnea. In patients receiving assist control ventilation (ACV) mode, increases in tidal volume, inspiratory flow, and positive end-expiratory pressure were subsequently tested. In patients on pressure support ventilation, increasing pressure support was first tested and then increasing the sensitivity of the inspiratory trigger. Arbitrarily, we considered that ventilator settings were involved in the pathogenesis of dyspnea when the postintervention VAS rating was lower than the preintervention level by at least 1 cm. The patients who fulfilled these criteria/responded to ventilator changes and nondyspneic patients were pooled into a common group that was subsequently compared with the group of patients whose dyspnea failed to recede in response to ventilator-setting adjustments.

Statistical Analysis. Nonparametric data were presented as median and interquartile range.

The main outcome was dyspnea, categorized as "present" or "absent" and therefore defining two groups of patients. They were compared using Fisher's exact test for qualitative variables and the Wilcoxon rank sum tests for quantitative variables. A multiple logistic regression with a backward stepwise model selection was used to identify the factors independently associated with dyspnea. All variables marginally associated with the main outcome at the 0.20 level were considered and sequentially removed from the model at the 0.05 level. Because dyspnea and anxiety are closely related, the logistic regression was repeated after exclusion of anxiety from the model. Paired Wilcoxon tests were performed to compare dyspnea, anxiety, and pain VAS before and after adjusting ventilator settings in the patients reporting dyspnea. Gray's test (18), with death on MV as a competing event, was used to compare median durations of MV between the two groups. All tests were two-sided, and p values $< .05$ were regarded as indicating statistical significance. The statistical analyses were performed using R 2.6.2 statistical package (The Foundation for Statistical Computing, Vienna, Austria).

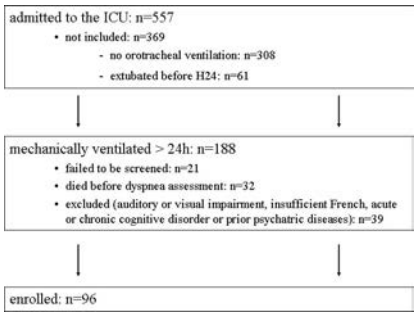

Figure 1. Flow chart of the study. *ICU,* intensive care unit.

RESULTS

Study Population. During the study period, 557 patients were referred to the two participating centers. One hundred eighty-eight were mechanically ventilated for >24 hrs (Fig. 1). Of those, 21 failed to be screened for various reasons, and 71 were excluded. Among those excluded, 39 patients were considered unable to accurately grade their dyspnea because of psychiatric, acute or chronic cognitive disorders or other reasons (insufficient command of French, visual or auditive impairment). Thirty-two other patients died before regaining consciousness.

Ninety-six patients (age 61 ± 18 yrs, 60% male) were included for final analysis (Table 1). The median duration of MV at the time of the study was 3 days (interquartile range, 1–6). The two main indications for MV were hypoxemic acute respiratory failure (mainly resulting from pneumonia) and the decompensation of an underlying neuromuscular disease (Table 1). Table 1 provides the variables

Table 1. Characteristics of the study population

Variable	Whole Cohort (n = 96)	Dyspnea (n = 45)	No Dyspnea (n = 51)	p
Male gender, no. (%)	60 (62)	29 (64)	31 (61)	.83
Median age (IQR), years	64 (48–73)	57 (43–72)	68 (52–73)	.24
Median Simplified Acute Physiology Score II at admission (IQR)	43 (31–60)	43 (29–60)	43 (33–56)	>.99
Indication for mechanical ventilation				.57
Hypoxemic acute respiratory failure, no. (%)	46 (48)	20 (45)	26 (51)	
Decompensation of an underlying neuromuscular disease, no. (%)	29 (30)	17 (38)	12 (24)	
Coma, no. (%)	10 (10)	4 (9)	6 (12)	
Chronic obstructive pulmonary disease, no. (%)	7 (7)	2 (4)	5 (9)	
Others, no. (%)	4 (4)	2 (4)	2 (4)	
Tracheotomy, no. (%)	17 (18)	7 (16)	10 (20)	.79
Median time from onset of mechanical ventilation (IQR), days	3 (1–6)	3 (1–6)	3 (1–6)	.23

IQR, interquartile range.

describing the patients at the time of the study. A tracheotomy had been performed before inclusion in 17 patients (18%).

Prevalence and Risk Factors for Dyspnea. Forty-five patients (47%) reported dyspnea. The median VAS dyspnea rating was 5 (interquartile range, 4–7). There were no significant differences between patients with and without dyspnea in terms of demographic variables, severity of critical illness, or indication for mechanical ventilation (Table 1). Body temperature, heart rate, and blood pressure were also similar in both groups. Anxiety and pain were more frequently reported by dyspneic patients than by nondyspneic ones (Table 2).

Dyspneic patients did not exhibit more frequent abnormalities in breathing dynamics or more frequent ausculatory abnormalities than nondyspneic patients (Table 2). This was also the case for chest radiograph abnormalities. There was no association between dyspnea and hemoglobin, the PaO_2/FIO_2 ratio, or $PaCO_2$ (Table 2). Dyspneic patients were more frequently mechanically ventilated with the ACV mode than nondyspneic patients (Table 2), but there was no other statistically significant difference regarding ventilatory settings (Table 2).

Multivariate analysis showed that dyspnea was independently associated with anxiety (odd ratio [OR], 8.84; 95% confidence interval [CI], 3.26–24.0; $p < .0001$), the ACV mode (OR, 4.77; 95% CI, 1.60–14.3; $p = .005$), and heart rate (OR, 1.33 per 10 beats/min; 95% CI, 1.02–1.75; $p = .038$). Removing anxiety from the model did not notably change the results (assist-control: OR, 3.92, 95% CI, 1.53–10.1, $p = .005$; heart rate: OR, 1.32, 95% CI, 1.05–1.68, $p = .019$).

Dyspneic Modalities. Among the 45 dyspneic patients, 15 chose only "air hunger" to characterize their respiratory discomfort, seven chose "excessive respiratory efforts," and six chose both these descriptors. Seven patients reported having breathing difficulties but did not choose between these two descriptors. This was not associated with any clear differences between patients, although five of the seven patients who chose "excessive respiratory efforts" only were under ACV with an inspiratory flow rate below 60 L/min^{-1}.

Role of Ventilator Settings and Potential Causes for Dyspnea. Adjustments in ventilator settings were performed by the physicians in charge of the patients in all those who reported dyspnea. Thirty-five percent of these patients met the "1-cm decrease in dyspnea rating" that was required to consider dyspnea responsive to adjustments in ventilator settings. The median reduction in dyspnea rating was −4.6 cm (95% CI, −6.1 to −3.2; $p = .0005$; Table 3). This dyspnea reduction was accompanied by a significant decrease in the VAS rating of anxiety (−1.7 [−3.3 to −0.2]; $p = .041$) but not in the VAS rating of pain (+0.3 [−0.7 to +1.2]; $p = .79$). In patients on ACV, increasing tidal volume and/or inspiratory flow was successful in partially alleviating dyspnea in ten cases (22% of dyspneic patients) and increasing positive end-expiratory pressure was successful in one case (2.2% patients). In patients on pressure support ventilation, increasing pressure support was successful in three cases (7%) and increasing the sensitivity of the inspiratory trigger was successful in one (2.2%).

In the 29 dyspneic patients in whom ventilator resetting was not successful, dyspnea was ascribed to a specific cause in only nine (31%) patients, including partial endotracheal tube obstruction (n = 3), atelectasis (n = 2), major pleural effusion (n = 2), severe acute anemia (n = 1), and pneumothorax (n = 1).

Clinical Outcomes. The median length of ICU stay was greater in the patients reporting dyspnea (8 [4–20] vs. 14 [8–28] days, $p = .017$). The median duration of MV from inclusion to extubation, the rate of successful extubation within the 3 days after inclusion, and mortality rate were all comparable between patients with and without dyspnea.

The occurrence of successful extubation within the 3 days after dyspnea assessment was significantly less frequent in the patients whose dyspnea failed to recede in response to ventilator setting adjustments than in the other patients (nondyspneic ones and those with a "responsive" dyspnea). The duration of MV was not statistically different between these two groups, whereas the length of stay in the ICU tended to be longer when dyspnea did not respond to ventilator adjustment (Table 4). In this category of patients, neuromuscular disease tended to be more frequent and chronic obstructive pulmonary disease less frequent. Age, Simplified Acute Physiology score II at admission, the duration of MV before inclusion, the intensity of dyspnea at baseline, PaO_2/FIO_2 ratio, and ventilator mode did not differ between the two groups (Table 4).

DISCUSSION

Among the findings of this study, we identify six salient elements regarding dyspnea in MV: its high prevalence; its intensity; its association with anxiety; its relationships with ventilator settings in one-third of cases; and its association with delayed extubation.

Frequency of Dyspnea. Approximately half of our patients indicated feeling dyspneic while mechanically ventilated (Tables 1 and 2), a frequency about twice that of pain. The physical signs collected, chest radiograph abnormalities, blood gases, and the hemoglobin level were not independently associated with dyspnea.

Table 2. Characteristics of the patients at the time of dyspnea assessment

Variable	Whole Cohort (n = 96)	Dyspnea (n = 45)	No Dyspnea (n = 51)	*p*
Anxiety, no. (%)	44 (46)	32 (71)	12 (24)	<.0001
If yes, median anxiety visual analog scale (IQR)	5 (4–7)	5 (4–7)	5 (4–6)	.64
Pain, no. (%)	28 (29)	19 (42)	9 (18)	.013
If yes, median pain visual analog scale (IQR)	5 (4–6)	5 (4–6)	5 (4–7)	.62
Median heart rate (IQR), beats/min	93 (81–107)	98 (82–107)	87 (76–106)	.15
Median respiratory rate (IQR), cycles/min	20 (17–25)	20 (18–28)	19 (17–24)	.14
Median temperature (IQR), °C	37.3 (36.9–37.7)	37.3 (37.0–37.7)	37.2 (36.9–38.0)	.86
Median systolic blood pressure (IQR), mm Hg	122 (110–137)	127 (110–140)	119 (108–134)	.15
Median diastolic blood pressure (IQR), mm Hg	71 (59–83)	73 (60–88)	69 (58–76)	.059
Abnormalities in breathing dynamics, no. (%)	22 (23)	11 (24)	11 (22)	.81
Normal auscultation, no. (%)	35 (36)	16 (36)	19 (37)	>.99
Median hemoglobin (IQR), g/dL	10 (9–12)	10 (9–13)	10 (9–12)	.92
Median PaO_2/FIO_2 ratio (IQR)	236 (176–318)	228 (152–318)	241 (191–317)	.42
Median $PaCO_2$ (IQR), mm Hg	41 (35–55)	42 (38–55)	40 (34–50)	.28
No radiograph abnormalities, no. (%)	25 (27)	13 (30)	12 (24)	.49
ACV, no. (%)	54 (56)	31 (69)	23 (45)	.024
Ventilator settings, no. (%)				.094
Pressure support ventilation; pressure support <15 cm H_2O	19 (20)	6 (13)	13 (25)	
Pressure support ventilation; pressure support ≥15 cm H_2O	23 (24)	8 (18)	15 (29)	
ACV; inspiratory flow <60 L/min	23 (24)	15 (33)	8 (16)	
ACV; inspiratory flow ≥60 L/min	31 (32)	16 (36)	15 (29)	
Median minute ventilation, L/min (IQR)	9 (8–12)	10 (8–12)	9 (7–13)	.87

IQR, interquartile range; ACV, assist-control ventilation.

Table 3. Effects of adjusting ventilator settings in the patients reporting dyspnea

Parameter	Mean Variation, cm (95% Confidence Interval)	*p*
Dyspnea VAS	−4.6 (−6.1 to −3.2)	.0005
Anxiety VAS	−1.7 (−3.3 to −0.2)	.041
Pain VAS	+0.3 (−0.7 to +1.2)	.79

VAS, visual analogic scale.

Ventilator settings were considered involved in the pathogenesis of dyspnea if and when the postintervention VAS rating was inferior by at least 1 cm to the preintervention one.

This indicates that, in this setting, dyspnea should be actively sought, yet in contrast to pain that is a major determinant of ICU-related posttraumatic manifestations (19), breathing difficulties are not listed among ICU stressors (20, 21). However, in one post-ICU recollection study, 22% of 75 patients remembered "not getting enough air from their endotracheal tube," something that bothered them "moderately or extremely" in 92% of cases (19). Recent data suggest that negative respiratory-related experiences can play an important role in the pathogenesis of ICU-related posttraumatic syndromes (22, 23). Of note, the prevalence of dyspnea in our patients might have been either overestimated because many of our patients had underlying respiratory disorders or underestimated because we did not perform repeated assessments.

Intensity and 'Quality' of Dyspnea. With VAS ratings of ≥4 in 70% of cases, dyspnea appeared to qualify as "moderate to intense." Similar pain ratings are an indication for analgesia (24). Only two verbal descriptors for their respiratory discomfort were proposed to our patients and we did not perform sophisticated psychophysical assessments. In particular, we did not attempt to separate the sensory and affective components of dyspnea (25). However, we note that they often chose "air hunger" to describe their respiratory sensation, which has been shown to be more unpleasant than the sense of excessive inspiratory effort for a given sensory intensity during experimental dyspnea (25). The very strong emotional impact of the ICU environment is a likely source of major dissociation between sensory and emotional components (26). This could have important implications in terms of care because sensory-affective discrepancies could explain either large effects of small interventions or conversely the failure of apparently adequate interventions to be efficient.

Dyspnea and Anxiety. Dyspnea strongly correlated with anxiety, which stresses the clinical relevance of the issue. Anxiety and dyspnea have never been concomitantly assessed in mechanically ventilated patients, previous studies having concentrated on the relationships between anxiety and other sources of MV-related discomfort such as extubation or suctioning (1, 16). The interplay between anxiety and dyspnea is complex and causative relationships can exist in both directions. Anxiety and fear stimulate ventilation and can thus produce dyspnea (7, 27). ICU and particularly MV are fearful experiences associated with diffuse anxiety (8) that can cause posttraumatic stress disorder (28, 29). In this view, some of the respiratory discomfort described by our patients could represent a nonspecific manifestation of anxiety. Anxiety-relieving interventions could thus have a positive effect on respiratory rhythm, as reported with music therapy (30). Reciprocally, dyspnea generates anxiety (1) and relieving dyspnea decreases anxiety (31). In line with this, anxiety significantly decreased in those of our patients who reported improvements after adjustments of the ventilator settings (Table 3). Therefore, relieving dyspnea is likely to have positive effects on anxiety. Like with anxiety, pain was more frequently experienced in dyspneic patients than in nondyspneic ones (Table 2). Pain also stimulates ventilation (32), and its control could possibly have beneficial effects on dyspnea. Because of this interrelationship, we believe that anxiety, dyspnea, and pain should be assessed systematically and together in mechanically ventilated ICU patients.

Role of Underlying Disease. Neuromuscular diseases may have been over-

Table 4. Characteristics and clinical outcomes as a function of the response of dyspnea to the adjustment of ventilator settings

	No Dyspnea or Positive Response to Ventilator Setting Adjustments (n = 67)	Absence of Response to Ventilator Setting Adjustments (n = 29)	*p*
Median length of intensive care unit stay (IQR), days	8 (4–23)	12 (9–24)	.091
Median duration of mechanical ventilation (IQR), days	5 (2–17)	7 (4–18)	.68[a]
No. (%) successful extubation within 3 days	27 (40)	5 (17)	.034
Indication for mechanical ventilation			.26
Hypoxemic acute respiratory failure, no. (%)	32 (48)	14 (48)	
Decompensation of an underlying neuromuscular disease, no. (%)	17 (25)	12 (41)	
Coma, no. (%)	8 (12)	2 (7)	
Chronic obstructive pulmonary disease, no. (%)	7 (10)	0 (0)	
Other, no. (%)	3 (4)	1 (3)	
Median dyspnea visual analog scale at baseline inclusion (if dyspnea) (IQR)	5 (5–7)	5 (2–7)	.11
Median Simplified Acute Physiology Score II at admission (IQR)	42 (33–58)	44 (26–60)	.88
Median duration of mechanical ventilation before inclusion (IQR), days	3 (1–6)	3 (1–6)	.67
Male gender, no. (%)	40 (60)	20 (69)	.49
Median age (IQR), yrs	67 (52–73)	54 (41–72)	.19
Median PaO_2/FIO_2 ratio (IQR)	236 (188–323)	238 (155–304)	.63
Assist-control ventilation, no. (%)	36 (54)	18 (62)	.51

IQR, interquartile range.

[a]Gray's test; $p = .15$ Wilcoxon test. The absence of response of dyspnea to the adjustment of ventilator settings was defined as the absence of a ≥1-cm reduction in the visual analog scale scoring of the dyspneic sensation after this adjustment.

represented in our study respective to previous surveys (33), because one of the centers (i.e., Raymond Poincaré Teaching Hospital) is specialized in the care of such patients. However, the prevalence of dyspnea, its intensity, and its characteristics did not seem to depend on the cause of respiratory failure. This suggests that dyspnea was not strongly related to mechanisms specific to the underlying respiratory disease. Indeed, patients with neuromuscular disease rather report excessive inspiratory effort resulting from weakness of respiratory muscles and consequent increased neuromotor output (34), whereas patients with chronic obstructive pulmonary disease tend to report air hunger that is ascribed to the hyperinflation-induced volume restriction and consequent neuromechanical uncoupling of the respiratory system (35, 36). However, we acknowledge that the small number of patients with chronic obstructive pulmonary disease patients in our population prevented us from observing such a relationship.

Contribution of Ventilator Settings. Dyspnea responded to changes in ventilator settings in 35% of our dyspneic patients, suggesting at least their partial responsibility. There was an independent association between dyspnea and the ACV mode, and five of the seven patients who chose "excessive respiratory effort" as the sole descriptor of their dyspnea received this ventilatory mode with an inspiratory flow <60 L/min. This is not surprising because this mode leaves almost no room for natural respiratory fluctuations and induces patient–ventilator dyssynchrony (37). Conversely, positive pressure-assisted ventilation (38), proportional-assisted ventilation (38), and negative pressure (39) in healthy subjects induce less dyspnea. However, a study by Knebel et al (12) reported that ACV and pressure support ventilation were equivalent in terms of dyspnea and anxiety. In our patients, the intervention that was the most often associated with dyspnea relief was an increase in inspiratory flow. This is in line with data from normal volunteers (40) in which low inspiratory flow is associated with higher inspiratory muscle energy expenditure (41) and high inspiratory flow optimizes respiratory muscle relaxation (42). Of note, since as early as 1994, clinical guidelines have mentioned the importance of setting high inspiratory flows during ACV (43). Low pressure support levels have also been associated with a sense of excessive inspiratory effort (44), and low tidal volumes are associated with air hunger in normal subjects (45) and in quadriplegics (46). We did not observe these associations in our patients, possibly as a result of the small size of the population, but this information must be kept in mind given the generalized use of low tidal volume ventilatory assistance.

We did not find any significant relationship between dyspnea and PaO_2, $PaCO_2$, MV-associated respiratory complications, anemia, etc. This does not mean that these factors are clinically unimportant on an individual basis, and larger studies will be needed to establish in what order and to what extent these elements must be taken into consideration in clinical practice.

Clinical Outcomes. In addition to a longer ICU stay in dyspneic patents, we observed that patients without dyspnea or in whom dyspnea responded favorably to the adjustment of ventilator settings were more often successfully extubated within the 3 subsequent days. This provides important clinical relevance to our setting adjustment procedure. We acknowledge that this procedure was rudimentary, leading to a possible underestimation of the number of patients in whom adjusting the ventilator could have been helpful. We also acknowledge that this finding should be confirmed in a larger cohort of patients in whom a weaning procedure would be standardized and controlled. Of note, both participating centers used the French guidelines on weaning (47) and that dyspnea and its fluctuations were not taken into account by the physician in charge of deciding when to extubate.

This finding also suggests that an intrinsic dyspnogenic factor delayed extubation in those patients whose dyspnea failed to recede after the adjustment of ventilator settings. In two-thirds of them, no specific cause of dyspnea was identified despite investigations that the physicians in charge of the patients decided to conduct. This calls for specific studies of which the aim would be to define what

has to be done to best identify the causative determinants of dyspnea during MV.

Finally, the association of dyspnea with delayed extubation suggests that the mere assessment of the patients' sensations could be useful not only for improving their comfort but to predict certain outcomes. Corroboration from larger cohorts is needed.

Limitations of the Study. This study was exploratory and does have limitations. First, we assessed respiratory sensations at a single time point. In particular, some patients may have experienced respiratory discomfort earlier, before full recovery from coma or sedation. Detecting respiratory-related suffering in patients who are not able to communicate verbally is of major importance and nonverbal metrics like Campbell's respiratory distress observation scale (48) or the identification of brain activities correlating to respiratory sensations provide interesting research avenues (49). Even with this limitation, we feel that messages like "half of the mechanically ventilated patients with whom it is first possible to communicate verbally report dyspnea" and "this is associated with clinical outcomes" are relevant primers for future research. Secondly, we only used a VAS to quantify dyspnea in our patients, proposing only two sensation descriptors (not validated in ICU patients) and we did not try to separate the sensory and affective components of dyspnea. These choices were made for the sake of simplicity, but it is true that they limit the interpretations that can be derived from our studies. Of note, VASs have been used to assess dyspnea in the ICU for the past 20 yrs (e.g., a study by Bouley et al [13] during weaning from mechanical ventilation and in the study by Powers et al [15]). This measure exhibited satisfactory intraclass correlation coefficients with the Borg scale and the face scale. Third, the study was observational on a modest population. The associations of dyspnea with clinical outcomes such as the length of ICU stay and weaning must therefore been taken with extreme caution. Only prospective interventional studies will determine whether dyspnea is an actual prognostic marker of such outcomes and whether interventions aimed at alleviating it are beneficial (like pain control reduces the durations of ventilatory support and ICU stay [50, 51]). Finally, our study population consisted only of medical critically ill patients. It would be of interest to assess dyspnea along with pain and anxiety in surgical critically ill patients in whom pain, surgery, and the use of opioids can affect respiratory sensation.

In conclusion, we suggest that the results of this study, although preliminary, are sufficient to raise some concern on behalf of clinicians about the respiratory comfort of their patients who receive mechanical ventilatory assistance. Indeed, it shows that dyspnea is frequent, often intense, correlated with anxiety, reduced by ventilator resetting in one-third of patients, and a possible marker of earlier extubation. It also shows that questioning mechanically ventilated patients is feasible and useful, in agreement with a recent study that demonstrates that patients' subjective perception of autonomous breathing is correlated with extubation success (52). We believe that taking account of patients' perception can only be beneficial in terms of the immediate comfort of the patients, the quality of the care provided by the ICU physician and nurses, and also probably in terms of distant consequences like posttraumatic experiences. Fully comprehending the physiological mechanisms and clinical consequences of dyspnea during MV and its long-term psychologic impact (8, 22, 23, 28, 29) will require a lot of additional work. This is necessary to clearly determine whether the benefits derived from potentially dyspnogenic ventilatory strategies are worth their dyspnea-related ransom.

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ANNEXE 2

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REVIEW

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Unrecognized suffering in the ICU: addressing dyspnea in mechanically ventilated patients

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Abstract *Background:* Intensive care unit (ICU) patients are exposed to many sources of discomfort. Although increasing attention is being given to the detection and treatment of pain, very little is given to the detection and treatment of dyspnea (defined as "breathing discomfort"). *Methods:* Published information on the prevalence, mechanisms, and potential negative impacts of dyspnea in mechanically ventilated patients are reviewed. The most appropriate tools to detect and quantify dyspnea in ICU patients are also assessed. *Results/Conclusions:* Growing evidence suggests that dyspnea is a frequent issue in mechanically ventilated ICU patients, is highly associated with anxiety and pain, and is improved in many patients by altering the ventilator settings. *Conclusions:* Future studies are needed to better delineate the impact of dyspnea in the ICU and to define diagnostic, monitoring and therapeutic protocols.

Keywords Pain management · Intensive care unit · Mechanically ventilated patients · Dyspnea · Therapeutic response

Dyspnea: an unrecognized cause of discomfort in mechanically ventilated patients?

Alleviating the immediate effects of pain suffered by patients is a natural mission of caregivers in all categories. In the intensive care unit, optimizing patient comfort is a major concern and involves three steps: (1) the identification of potential discomfort, (2) the diagnosis of the reason for this discomfort, and (3) the initiation of a therapeutic response to treat this discomfort. Although mechanically ventilated ICU patients cannot communicate easily, it is possible to communicate with many of them and possible to guess at discomfort from observations in the remainder. Identifying the reason for the discomfort can be challenging because discomfort in these patients can be due to many causes (Fig. 1), and it is crucial to that the cause of the discomfort be correctly identified since each potential cause of discomfort leads to a different therapeutic response. Pain is one of the major causes of discomfort in ICU patients and has

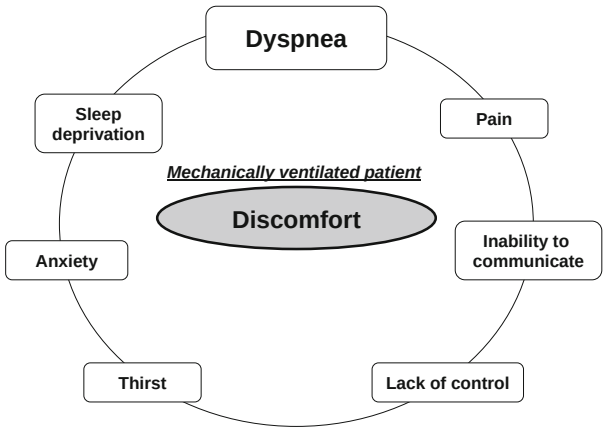

Fig. 1 Possible reasons for discomfort in mechanically ventilated patients

received major attention during the past decade with beneficial effects on long-term outcomes. Awareness of pain and its proactive management has resulted in improved ICU outcomes [1, 2].

Although dyspnea and pain share many similarities [3–5], little attention has been given to assessing and managing dyspnea; little rigorous research data are available and there are currently no clinical guidelines for managing dyspnea in the ventilated patient. However, dyspnea can be assessed, and available data do show that it frequently causes discomfort in mechanically ventilated patients admitted to the ICU.

ICU patients are exposed to many stimuli that can generate or exacerbate dyspnea. In addition to underlying cardiopulmonary abnormalities, respiratory discomfort may be caused by some of the therapeutic management strategies that have been adopted in recent years. These include lowering sedation [6], preserving spontaneous breathing activity [7], and the use of low tidal volumes [8] even in the absence of severe lung disorders [9–11]. It cannot be ruled out that sedation may give a falsely reassuring outward appearance of comfort in patients actually suffering from undiminished—or even increased—respiratory discomfort, as in the case of pain [12, 13]. For example, pain ratings and pain-related cortical activations in response to cutaneous pain stimuli are increased by moderate propofol sedation. Strong pain-related activations remain in some cortical regions even during heavy propofol sedation that renders subjects unresponsive.

The aim of this review is to promote awareness in ICU caregivers of the unrecognized problem of dyspnea. Herein we summarize current knowledge on the prevalence of dyspnea in mechanically ventilated ICU patients and on the corresponding risk factors. We also discuss possible approaches to detect and quantify dyspnea in these patients.

Simplified physiological basis of dyspneic sensations

The physiology of dyspnea has been extensively reviewed [14–17]. The neurophysiological basis of dyspnea is more complex than that for many other sensations and involves both excitatory and inhibitory afferent inputs from sensory nerves as well as the perception of motor commands (so-called corollary discharge). In mechanically ventilated patients, it seems reasonable to focus on two main dyspnea modalities, namely “air hunger” and “excessive work/effort of breathing”.

Air hunger

Air hunger (an unpleasant, unsatisfied urge to breathe) is perhaps the most distressing dyspnea modality [18, 19] and is characterized by such verbal expressions as “I am not getting enough air”, “I feel that I am suffocating”, and “I need more air”. Experiments in paralyzed subjects (complete neuromuscular block in normal volunteers [18] or C_1–C_2 quadriplegic patients [20]) have shown that an acute rise in $PaCO_2$ (arterial carbon dioxide tension) suffices to induce air hunger independent of any respiratory muscle activity. Air hunger also increases when the tidal volume is decreased under mechanical ventilation and the $PaCO_2$ is held constant [21, 22]. Air hunger appears to arise from a “corollary discharge” or copy of the automatic efferent command from the brainstem respiratory motor center. The brainstem respiratory center is excited by various stimuli that “drive” respiration hypercapnia, hypoxia, exercise, and hyperthermia. Even when respiratory drive is held constant, air hunger is relieved by tidal expansion of the lungs [23]. The principle pathway for this volume expansion relief is pulmonary stretch receptor afferents [22], although a contribution from chest wall afferents has not been ruled out [24]. Thus, air hunger develops when there is an imbalance between the efferent and the inhibitory afferent messages. This imbalance triggers activity in interoceptive areas of the brain involved in unpleasant sensations (such as visceral pain, thirst, or hunger), particularly the insular cortex, amygdala, and anterior cingulate [21]. In contrast, when increased ventilatory drive is matched by an adequate stretch receptor return from the lungs, respiratory sensations will not necessarily be perceived as uncomfortable and will therefore not qualify as dyspnea (e.g., during moderate exercise in healthy persons).

Excessive work/effort of breathing

This dyspnea modality is characterized by such verbal expressions such as “My breathing requires effort”, “My breathing requires more work” [25], “I have difficulty

breathing", "I need to make an effort to get the air in", and "I must concentrate on my breathing". It arises from a sense of excessive breathing effort even when gas exchange needs are adequately met—this sense of work or effort arises in both the muscle afferents of the chest wall and the diaphragm, from volitional respiratory motor centers in the neocortex, and perhaps from automatic respiratory motor centers. Dyspnea of the excessive work/effort type characteristically occurs when there is an imbalance between the load imposed upon the respiratory muscle (respiratory impedance) and the capacity of these muscles to overcome this load [26]. This can correspond to deteriorated respiratory mechanics, a weakening of inspiratory muscles, or the combination of both. Dynamic hyperinflation in patients with chronic obstructive pulmonary disease (COPD) provides a typical example of such situations. Dynamic hyperinflation combines an increased respiratory impedance (increased lung elastance at high lung volume requiring high inspiratory muscle force) and a functional weakening of inspiratory muscles [hyperinflation-related shortening that places the muscles at disadvantage both mechanically (e.g., flattened diaphragm) and on the length–tension curve]. In addition, patients must overcome the resultant intrinsic positive expiratory pressure before beginning to move air and trigger the ventilator, thereby imposing an inspiratory threshold load. Neuromuscular disorders involving the respiratory muscles can also give rise to dyspnea of the excessive work/effort type. Adequate ventilatory support should prevent this type of dyspnea, the very purpose of ventilatory assistance being to adjust the load/capacity balance of the respiratory system.

Complex sensations

Patients mechanically ventilated for acute respiratory failure generally experience mixed respiratory sensations (Fig. 2). Increased respiratory impedance, often associated with decreased respiratory muscle strength, generates a sense of excessive respiratory work/effort, and the corresponding failure to maintain gas exchange combined with inadequate tidal volume is a source of air hunger. It is therefore expected that dyspneic ICU patients will report more than one dyspnea modality [27].

Differential affective components

Dyspnea, like pain, can be viewed as causing an immediate feeling of unpleasantness as well as having more complex emotional sequelae [28]. Recent experimental data have demonstrated that both unpleasantness and emotional response can be differentially altered with changes in the dyspnea modality or drug treatment. At a similar level of sensory intensity, air hunger elicits more unpleasantness than excessive work/effort and is associated with greater feelings of anxiety and fear [19]. Of clinical relevance is the experimental finding that an effective way to induce air hunger is to increase ventilatory demand via mild hypercapnia while hindering the normal ventilatory response [29, 30]. Likewise, therapeutic interventions can have different effects on both the sensory and affective component of dyspnea [31].

What are the main determinants of dyspnea in mechanically ventilated patients?

The determinants of dyspnea in mechanically ventilated patients are multifactorial, with contributions from the intrinsic bronchopulmonary status of the patients, ventilator settings, various healthcare activities, extrinsic physiological stimulations of the ventilatory drive, and non-respiratory factors such as anxiety or pain. Several of these factors can coincide at any particular moment, and their effects are likely to be synergistic.

Intrinsic cardiopulmonary status

Although the disease that has required ventilatory assistance is the usual cause of dyspnea, mechanical ventilation has the potential to reduce or eliminate the dyspnea. An increase in dyspnea during the course of mechanical ventilation can signal a problem with the mechanical ventilation itself or signal an adverse event, such worsening respiratory mechanics and/or the ventilation–perfusion equilibrium [pneumothorax, atelectasis, ventilator-associated pneumonia, hydrostatic pulmonary edema or acute respiratory distress syndrome (ARDS)] or a non-respiratory one (acute hemorrhage, sepsis, or worsening heart failure) [27].

Ventilator settings

The authors of the largest study dealing with dyspnea in ICU mechanically ventilated patients conducted to date [27] reported that ventilator adjustments targeted at dyspnea reduction significantly improved respiratory comfort, often dramatically, in 35 % of their mechanically ventilated patients who reported dyspnea. In addition, their data suggest that ventilator mode played a role in dyspnea since dyspneic patients were more likely to be ventilated with assist-control ventilation (ACV) than non-dyspneic patients (69 vs. 45 %), and the multivariate analysis showed that ACV was independently associated with dyspnea [odds ratio (OR) 4.77, 95 % confidence interval (CI) 1.60–14.3] [27]. This difference may be due

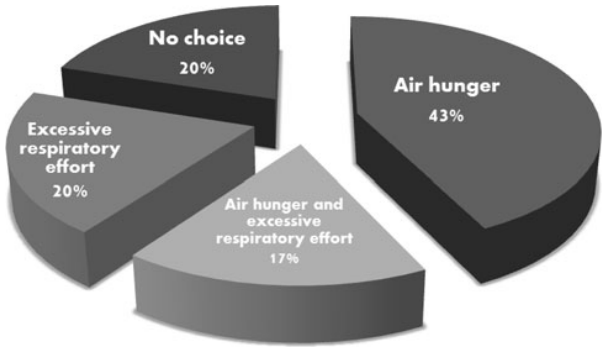

Fig. 2 Modality of dyspnea experienced by ventilated patients (data from Schmidt et al. [27])

to the fundamental characteristics of the ventilatory mode, but is more likely due to the greater ease in optimizing ventilatory parameters during support. Unfortunately, little is known about the effect of ventilator mode per se, as the studies conducted on this problem have failed to measure or control for variables known to alter dyspnea, such as tidal volume, arterial $PaCO_2$, and inspiratory flow rate, among the different modes [32].

It is likely that tidal volume changes alone can explain the observed differences between ventilator modes. Indeed, when we re-plotted the data from two studies to show dyspnea ratings versus tidal volume [33, 34], we noted that ratings from different modes fell along the same line (Fig. 3). This is an important issue since recent publications argue that tidal volume should be minimized in mechanically ventilated patients, even in those without risk factors for ARDS [9–11]. When setting tidal volume the healthcare professional should also be aware of the resultant discomfort and potentially deleterious effects of the settings. Optimization of flow rate also influences respiratory comfort [27], consistent with earlier findings in healthy subjects [35, 36].

Finally, during inspiratory pressure support, there seems to be a U-shaped relationship between the level of assistance provided and dyspnea; if assistance is either too high or too low discomfort increases [37].

Patient–ventilator interface; respiratory and non-respiratory care activities

The patient–ventilator interface can induce discomfort, be it an endotracheal tube [38, 39] or a face mask [40]. Beyond this, the results of the small descriptive case study by Lush et al. [41] indicate that many other events can be associated with dyspnea, such as turns, transfers, or bathing, but also the presence of the physicians or external events, such as shift changes or a death elsewhere in the unit.

Extrinsic physiological stimulations of ventilatory drive

Respiratory drive in excess of achieved ventilation is the cause of air hunger (see above, physiological basis). Fever, acidosis, or anemia are frequent causes of increased ventilatory drive in ICU patients, and should therefore be looked for in the presence of apparently unexplained dyspnea.

Anxiety and pain

Anxiety and pain may increase dyspnea by stimulating ventilatory drive [42], and it is also likely that these factors can also interact with the affective dimension of dyspnea. In the dyspnea–ICU study carried out by Schmidt et al. [27], pain and anxiety were more frequent in dyspneic than in non-dyspneic mechanically ventilated patients. Anxiety was independently associated with dyspnea (OR 8.84, 95 % CI 3.26–24–14.3), and it was responsive to ventilator settings adjustments when these changes relieved dyspnea. This result points towards a bidirectional causative relationship between anxiety and dyspnea.

Prevalence of dyspnea in mechanically ventilated patients

Because dyspnea can only be perceived by the person experiencing it, it should be assessed by questioning the patient; only when communication with the patient is impossible should the clinician rely primarily on outward signs. We describe the assessment of dyspnea in more detail in following sections. There is a paucity of published data on dyspnea prevalence in mechanically ventilated patients, and clinical experience suggests that dyspnea is not routinely assessed and recorded. Studies in which patients have been asked to recall their ICU experience give insights into the magnitude of the problem. For example, Rotondi et al. [38] were able to explore the recollections of 150 patients who had survived an ICU stay during which they had been mechanically ventilated for ≥2days. Two-thirds of these patients remembered the endotracheal tube (ETT) of whom 45 % recalled “feeling choked by the ETT” and 24 % remembered “not getting enough air from the ETT”. ETT-related experiences were considered stressful and were strongly associated with the occurrence of spells of terror or “feeling nervous when left alone” [38]. In a different study involving 126 COPD patients who were interviewed at the time of their discharge from the ICU stay, 90 % recalled experiencing traumatic events during their stay in the ICU [40]. “Suffocation” was the second most frequently noted item

(55 % of the respondents) just behind "sleep disorders" (63 %) [40]. To our knowledge, dyspnea in mechanically ventilated patients has been the main research focus of only eight prospective studies published to date (Table 1; [27, 41, 43–48]).

Four of these studies focused on breathing comfort in the context of weaning trials [44–46, 48], but they also provide pre-weaning dyspnea assessments. In this setting, dyspnea was common, although the exact proportion of patients who were dyspneic before weaning was not systematically reported. In one study [46], the authors explored the relationship between dyspnea and pre-weaning mood state in 21 mechanically ventilated patients using a shortened version of the profile of mood states (sPOMS) [49]. Weak relationships were found between dyspnea intensity [visual analog scale (VAS)] and mood states, with the "vigor" subscore of the sPOMS being the closest to reach a statistically significant negative correlation with the intensity of dyspnea ($p = 0.07$) [46].

The other four prospective studies evaluated dyspnea in alert mechanically ventilated patients not having entered the weaning process [27, 41, 45, 47]. The study by Lush et al. [41] has a descriptive case design and pertains to a convenience sample of five individuals. Dyspnea was systematically assessed by specially trained nurses every 4 h. All patients reported dyspnea at some time during the study, with a VAS intensity reaching 95 % of full scale in some cases. Weak correlations were found between dyspnea intensity and several physiological variables, such as PaO_2, $PaCO_2$, or ventilation. Stronger correlations were found between dyspnea intensity and the density of events and activities occurring in the ICU at the time of dyspnea evaluation—whether or not these events were directly related to patient care (examples of variables recorded include "change of shift", "engineers in the unit", "death next bed", among others). The study by Karampela et al. [47] tested the "feasibility of incorporating a dyspnea evaluation protocol into bedside assessments routinely performed by respiratory therapists". Systematic dyspnea assessment ("Are you feeling short of breath right now"; "Is your shortness of breath mild, moderate, or severe?") was performed at 4-h intervals in 238 patients, leading to a database of 2,539 patient–respiratory therapist encounters. Dyspnea was evaluated according to protocol in 74 % of

Table 1 Prospective dyspnea studies in mechanically ventilated patients

Study	Number of patients	Frequency of dyspnea assessment	Total number of assessments	No. of dyspneic patients (%)	Dyspnea Visual Analog Scale (%FS)	Notes
Knebel et al. [44] Connelly et al. [46]	21	Repetitive	40	NA	32 ± 22	Compares dyspnea on SIMV and PSV during the weaning period. Dyspnea during SIMV/PSV predicted weaning success ($p < 0.05$). Explores pre-weaning mood state and dyspnea in mechanically ventilated patients
Bouley et al. [43]	9	Repetitive	90	NA	NA	Compares dyspnea experienced by ventilator-dependent patients receiving SIMV versus T-piece or PSV weaning. Findings indicated no difference in the degree of dyspnea experienced between weaning methods
Karampela et al. [47]	238	Repetitive	600	11	NA	Tests feasibility of incorporating a dyspnea evaluation protocol into bedside assessments routinely performed by respiratory therapists on mechanically ventilated patients
Twibell et al. [48]	68	Single time	68	NA	35 ± 28	Compares dyspnea on SIMV and PSV during weaning. Dyspnea was associated with physiological variables but not with weaning outcomes
Lush et al. [41]	5	Repetitive	189	100	NA	Impact of environment variables as ICU environment, patient activities or events with dyspnea
Powers et al. [45]	28	Repetitive	53	50	52 ± 17	Methodological study evaluating test-retest reliability of 5 dyspnea rating scale
Schmidt et al. [27]	96	Single time	96	47	50 (40–70)	Dyspnea was significantly associated with anxiety, assisted control ventilation, and heart rate. Adjusting ventilator settings alleviated dyspnea in 35 % of patients

Visual analog scale (VAS) results are given as mean ± standard deviation (SD) or as the median with the 25–75 interquartile range given in parenthesis

%FS % Full scale, *ICU* intensive care unit, *SIMV* synchronized intermittent mandatory ventilation, *PSV* pressure support ventilation, *ICU* Intensive Care Unit, *NA* not available

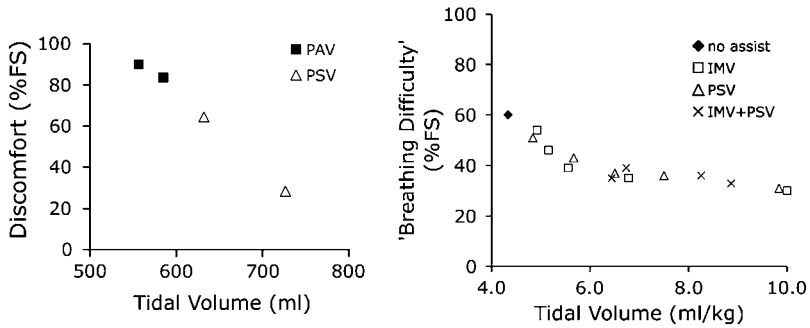

Fig. 3 Relationship between dyspnea and tidal volume. Data are re-plotted from Mols et al. [34] (*left*) and Leung et al. [33] (*right*). Although the authors of both papers reported a difference in respiratory comfort dependent on ventilator mode, these plots suggest that the main effect of changing mode is to change the tidal volume delivered by the ventilator. Consequent changes in pulmonary stretch receptor activity as well as blood gasses are in the correct direction to explain the observed effects on discomfort ratings. *PAV* Proportional assist ventilation, *PSV* pressure-support ventilation, *IMV* intermittent mandatory volume ventilation, *dyspn unassist* unassisted breathing, *%FS* % full scale

the cases, with 32.1 % of the patients being adequately alert to answer questions during encounters ($n = 600$). Dyspnea was assessed to be present in 11 % of the cases and was characterized as moderate to severe in one-third of these. The study by Powers et al. [45] was designed to evaluate the "test–retest reliability of five dyspnea rating scales" and to examine the "correlations between each of these 5 rating scales and physiological measures of respiratory function". Within a convenience sample of 28 patients, 50 % reported dyspnea, with a median VAS rating of 52 % of full scale. Finally, Schmidt et al. [27] studied 96 alert mechanically ventilated patients cared for at two separate ICUs; of these patients, 47 % reported dyspnea, with a median VAS measure of 50 % of full scale. This study was the first to explore the modality of dyspnea experienced by ventilated patients. When asked to describe their dyspnea as either "air hunger" or "excessive work/effort"; 56 % of the dyspneic patients chose "air hunger" only; 16 % chose "excessive work/effort" only; 13 % chose both "air hunger" and "excessive work/effort"; the remaining patients were unable to make a choice (Fig. 2).

The available set of data on dyspnea in mechanically ventilated patient is very limited in size and is heterogeneous in quality. It suggests that the frequency of this clinical issue is sufficiently high to make it worthy of attention. The next important question relates to the clinical relevance of being dyspneic under mechanical ventilation.

Clinical relevance of dyspnea in mechanically ventilated patients

Immediate suffering

Dyspnea is a noxious sensation. With VAS ratings of generally around 50 % of full scale [27], dyspnea in mechanically ventilated patients qualifies as "moderate to intense". It can however reach unbearable levels [40]. Similar pain ratings constitute a clear indication for the administration of analgesics [50].

Dyspnea causes anxiety [51]. In the study by Schmidt et al. [27] discussed above, dyspneic patients were more likely to present with anxiety than non-dyspneic patients (71 vs. 24 %, respectively), and dyspnea was independently associated with anxiety (OR 8.84, 95 % CI 3.26–24.0, $p < 0.0001$). Experimental dyspnea produces anxiety even in healthy subjects who know they are safe and disease-free [19, 52]. The interplay between anxiety and dyspnea is complex, and causative relationships can exist in both directions.

Delayed psychological sequelae

As mentioned above, patients' recollections of their ICU experience point to dyspnea during mechanical ventilation as a major ICU stressor [38, 40]. Dark "respiratory recollections" may persist for several weeks. Bergbom-Engberg and Haljamae [51] studied 158 patients who had been mechanically ventilated during an ICU stay and who could remember the treatment. When questioned 2–48 months after discharge, 47 % of these patients reported having felt anxiety and/or fear during mechanical ventilation. Respiratory difficulties (e.g. "to synchronize with the respirator…") were among potent drivers of feelings of anxiety, fear, agony, panic, and insecurity.

Post-traumatic stress disorder (PTSD) is now recognized as a common sequel of the ICU experience [53–56]. Recalled dyspnea has been found to be associated with PTSD in ICU survivors [54], and the PTSD symptom score in the post-ICU population has been found to be significantly correlated with the duration of mechanical ventilation [55].

Impact on ICU stay outcomes

Dyspnea during mechanical ventilation may be useful to predict weaning outcome and ICU length of stay. In the study of Schmidt et al. [27], successful extubation within 3 days of the assessment of dyspnea was significantly less frequent in patients whose dyspnea failed to recede following the adjustment of the ventilator settings than in the patients whose dyspnea improved after ventilator adjustment.

The impact of dyspnea on ICU outcomes and on PTSD is strongly suggested by correlative data, but needs to be clarified with interventional trials. Until this link is disproved, the sensible and compassionate approach is to identify and alleviate dyspnea in mechanically ventilated patients.

Assessing dyspnea in the mechanically ventilated patient

The 2012 statement on dyspnea by the American Thoracic Society emphasizes strongly that "…dyspnea *per se* can only be perceived *by the person experiencing it*. Perception entails conscious recognition and interpretation of sensory stimuli and their meaning. Therefore, as is the case with pain, adequate assessment of dyspnea depends on self-report" [14]. The first step in managing dyspnea is therefore to ask the patient what he or she feels. One may obtain verbal or written responses to appropriate questions and/or responses to rating scales; if these fail, indirect means should be used to assess the pain.

Direct approach: guided questioning and rating scales

Clinical practice shows that conscious mechanically ventilated patients are able to answer simple questions about their respiratory sensations, even when they are slightly confused, cognitively impaired, or unable to speak due to an endotracheal tube. It is useful to start with a qualitative approach using questions phrased to allow simple yes/no answers, such as "is your breathing OK?", "do you have difficulties breathing?", "is your breathing comfortable?".

Most awake patients can respond appropriately to pain and dyspnea scales, which can provide considerably more useful information than binary responses. Rating scales provide a quantitative measure that can be tracked over time in the same patient and can be statistically tested when various parameters are being assessed, such as treatment effects, clinical unit performance, among others. In mechanically ventilated patients, dyspnea can be measured using available psychometric tools. Single-dimension dyspnea scales include the classical VAS, the modified Borg scale, a numerical ordinal scale, and the faces pain scale. Powers and Bennett [45] tested all of these scales in a small population of mechanically ventilated patients and found the Test–retest reliability and intraclass correlation to be satisfactory [45]. In patients who cannot manipulate those tools themselves for any reason, it is easy for caregivers to provide adequate help. This option was explicitly offered in the study by Schmidt et al. [27] and no problems were reported. Of note, VAS have been used in mechanically ventilated patients to assess pain, anxiety, and the sense of inspiratory effort under different ventilatory assistance modalities [57].

Indirect approach: clinical surrogates

When the patient is unable to report his or her dyspnea, clinical surrogates of dyspnea would be useful. In mechanically ventilated patients, individual clinical signs correlate poorly with dyspnea ratings [27], contrary to the case in spontaneously breathing patients with acute respiratory failure. A composite observation scale such as the Respiratory Distress Observation Scale (RDOS) may be useful [58, 59]. This scale comprises weighted measures of heart rate, respiratory rate, the use of inspiratory neck muscles to breathe, the presence of paradoxical abdominal movement during inspiration, the degree of restlessness, the presence of end-expiratory grunting and nasal flaring, and, importantly, the presence of a fearful facial display. In studies of pulmonary rehabilitation patients and palliative care patients, the RDOS has been shown to correlate with VAS ratings and exhibit internal consistency and discriminant validity with pain [58]. The RDOS has also been found to respond to treatment, including treatment in patients who had been unable to self-describe their dyspnea [59]. However, the RDOS has only been validated in spontaneously breathing patients and needs to be adapted and validated for ventilated ICU patients because several of the vital sign variables are likely to be disturbed by medications and mechanical ventilation in ICU patients.

Patient–ventilator dyssynchrony can be observed clinically and through the inspection of the ventilator-derived pressure and flow waveforms. How dyssynchrony relates to dyspnea is unclear. Indeed, patient–ventilatory asynchrony studies seldom mention dyspnea. Of note, situations typically associated with patient–ventilator asynchronies, such as over-assistance in patients with COPD, are likely to be associated with a strong central neural inhibition [60] that could, paradoxically, "protect" from dyspnea [61].

Electrophysiological surrogates

Physiological surrogates of neural respiratory drive based on flow, volume, and respiratory muscle pressure

generation usually underestimate the levels of neural respiratory drive in patients with compromised respiratory mechanics [62]. Because they are not influenced by respiratory mechanics, electrophysiological indices may be better indices of the neural drive from respiratory motor centers. As mentioned above, a corollary copy of respiratory motor drive is thought to be an important excitatory input to dyspnea and, therefore, a good measure of respiratory motor drive may help to infer dyspnea. It should be remembered, however, that severe discomfort arises not from drive alone, but from a failure of ventilation to match drive.

Electromyographic approach

The electromyographic activity (EMG) of the diaphragm and of the extra-diaphragmatic inspiratory muscles has often been used as a measure of respiratory center motor drive [63–65]. The results of several studies conducted in healthy subjects and in patients suggest that inspiratory muscle EMG measurements could provide a surrogate neurophysiological biomarker of dyspnea [61, 64, 66–69]. These observations have been validated in ICU patients [61, 70].

Electroencephalographic approach

Normal individuals faced with external inspiratory loading exhibit a respiratory-related premotor cortical activity that can be described using electroencephalographic tools (EEG) [71]. Raux et al. also observed this activity in patients on non-invasive mechanical ventilation when respiratory discomfort was induced through the use of inappropriate ventilator settings [72]. This premotor activity was correlated with respiratory discomfort under the circumstances of these experiments [72]. Although causal relationship between this cortical activity and dyspnea remains to be established and although ICU data have not yet been published, "respiratory-related EEG" could also provide a surrogate neurophysiological biomarker of dyspnea in the ICU.

Conclusions

Dyspnea in mechanically ventilated ICU patients is an under-recognized issue. We suggest that assessment and management of dyspnea in these patients has the potential to minimize suffering, reduce the use of sedation, and reduce ICU-related PTSD. We therefore suggest that future studies should aim to (1) provide tools to evaluate dyspnea in patients who cannot respond to questioning; (2) directly evaluate the impact of dyspnea in ICU patients; (3) determine the efficacy of strategies aimed at minimizing dyspnea, ranging from improved ventilation strategies to pharmacologic interventions.

Conflicts of interest None.

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RESUME

En ventilation assistée, l'inadéquation entre l'activité des muscles respiratoires du patient et l'assistance délivrée par le ventilateur se traduit par la survenue d'une dysharmonie patient-ventilateur potentiellement associée avec la survenue d'asynchronies patient-ventilateur et d'une dyspnée. Minimiser cette dysharmonie est un objectif majeur de la ventilation assistée. Le Neuro Asservissement de la Ventilation Assistée (NAVA) et la Ventilation Assistée Proportionnelle (PAV) sont deux nouveaux modes qui pourraient améliorer l'harmonie patient-ventilateur.

Nous avons montré que, de façon similaire, le NAVA et la PAV diminuent le nombre d'asynchronie patient-ventilateur, préviennent la surdistension pulmonaire, restaurent la variabilité cycle à cycle du comportement ventilatoire et améliorent l'équilibre charge-capacité et le couplage neuromécanique. De plus, l'utilisation du mode NAVA en ventilation non invasive pourrait également permettre d'améliorer la synchronisation patient-ventilateur.

Nous avons également montré aux cours de différents travaux sur la dyspnée en ventilation mécanique que celle ci était fréquente mais néanmoins difficile à identifier, en particulier chez les patients non communicants. L'EMG de surface des muscles inspiratoires extra-diaphragmatiques pourrait constituer un outil simple et objectif pouvant permettre au clinicien de diagnostiquer une dyspnée en ventilation mécanique et optimiser les réglages du ventilateur dans le but de minimiser la dysharmonie patient-ventilateur.

Ces données permettent de progresser vers une meilleure connaissance de la dysharmonie patient-ventilateur. L'impact clinique de l'utilisation des modes proportionnels et d'une détection précoce de la dyspnée doit maintenant être évalué par des essais cliniques.

MOTS CLES : Neuro Asservissement de la Ventilation Assistée, Ventilation Assistée Proportionnelle, asynchronie, confort, dyspnée, électromyogramme

ABSTRACT

Ventilatory support must be tailored to the load capacity balance of the respiratory system to avoid patient-ventilator dysharmony as it may lead to patient-ventilator asynchronies and dyspnea. Minimizing this dysharmony is crucial. Neurally Ventilatory Assist Ventilation (NAVA) and Proportional Assist Ventilation (PAV) modes may improve patient-ventilator interaction.

We showed in this work that PAV and NAVA both prevents overdistension, restores breath by breath variability of the breathing pattern and improves neuromechanical coupling and patient-ventilator asynchrony in fairly similar ways compared to pressure support ventilation. In addition the use of NAVA with non-invasive ventilation may also improve patient-ventilator interaction.

We also demonstrated that dyspnea is a frequent issue in mechanically ventilated ICU patients and it can be difficult to assess when the patient is unable to report it. Surface electromyograms of extradiaphragmatic inspiratory muscles provides a simple, reliable and non-invasive indicator of respiratory muscle loading/unloading in mechanically ventilated patients. Because this EMG activity is strongly correlated to the intensity of dyspnea, it could be used as a surrogate of respiratory sensations in mechanically ventilated patients, and might, therefore, provide a monitoring tool in patients in whom detection and quantification of dyspnea is complex if not impossible.

These data provide a better understanding of patient-ventilator dysharmony. Further studies are needed to evaluate the possible clinical benefits of NAVA and PAV on clinical outcomes and the impact of an early detection of dyspnea in mechanical ventilation.

KEY WORDS : Neurally Ventilatory Assist Ventilation, Proportional Assist Ventilation, patient-ventilator asynchrony, comfort, dyspnea, surface electromyogram.