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Implication respective des composantes sensorielles, émotionnelles et affectives dans le soulagement de la dyspnée chez les patients de réanimation

Par Côme Bureau

Thèse de doctorat de Physiologie, Physiopathologie et Thérapeutique

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Liste des abréviations:

EVA : échelle visuelle analogique

BPCO : bronchopneumopathie chronique obstructive

ECMO : circulation extracorporelle

ECMOva : circulation extracorporelle veino-artérielle

EMG : électromyogramme

IA : indice d'asynchronie

IC-RDOS : Intensive Care - Respiratory Distress Observation Scale

MDP : Multidimensional Dyspnea Profile

NAVA : Neurally Adjusted Ventilatory Assist

P0.1 : Pression d'occlusion des voies respiratoires

PAV : ventilation assistée proportionnelle

RDOS : Respiratory Distress Observation Scale

SSPT : syndrome de stress post traumatique

VSAI : ventilation spontanée avec aide inspiratoire

Introduction

La dyspnée est une sensation subjective caractérisée par un inconfort respiratoire. Ce symptôme altère la qualité de vie des patients qui en souffrent. Elle est définie par l'American Thoracic Society comme « une expérience subjective d'inconfort respiratoire qui consiste en des sensations qualitativement distinctes dont l'intensité varie » (1). Il s'agit d'une sensation multimodale qui intègre à la fois des facteurs psychologiques, sociaux et environnementaux (2).

En réanimation, jusqu'à la moitié des patients sous ventilation mécanique présentent une dyspnée dont l'intensité est telle que, s'il s'agissait d'une douleur, elle impliquerait une réponse thérapeutique immédiate (3, 4). La dyspnée est décrite par ces patients comme l'un des pires souvenirs de leur séjour en réanimation notamment la sensation d'étouffement. Au-delà de la souffrance immédiate qu'elle induit, la dyspnée semble associée à l'allongement de la durée de ventilation mécanique et expose les patients au risque de séquelles neuropsychiques de la réanimation, telles que la survenue d'un syndrome de stress post-traumatique.

Si les mécanismes impliqués dans la genèse de la dyspnée sont de mieux en mieux connus ; ce n'est pas le cas de ceux impliqués dans son soulagement.

L'objectif de cette thèse est d'une part de mieux comprendre les mécanismes impliqués dans le soulagement de la dyspnée, d'autre part d'étudier chez des patients de réanimation des thérapeutiques visant à soulager la dyspnée au moyen d'interactions avec les récepteurs ou processus d'intégration impliqués dans sa genèse.

La thèse se compose de deux parties.

Dans sa première partie, cette thèse se propose : 1) de discuter de l'état actuel des connaissances sur les mécanismes impliqués dans la genèse de la dyspnée et les thérapeutiques disponibles pour la soulager chez les patients de réanimation ; 2) de présenter une description des options thérapeutiques (ventilation assistée proportionnelle et circulation extracorporelle) utilisées pour le besoin des études constituant la seconde partie de la présente thèse ; 3) d'examiner les techniques d'investigation de la dyspnée et de la commande centrale respiratoire.

La seconde partie de la thèse est organisée autour de quatre travaux : deux articles publiés, un article soumis et un article finalisé qui sera prochainement soumis. A partir de ces travaux nous décrirons le lien entre, d'une part l'intensité de la dyspnée, marqueur de l'intensité de la commande respiratoire centrale et donc indirectement de l'équilibre charge – capacité, et, d'autre part l'activité électromyographique du diaphragme et des muscles inspiratoires extradiaphragmatiques (**Chapitre 1**). Nous étudierons ensuite l'impact sur la dyspnée de trois interventions modifiant les processus d'intégration impliqués dans sa genèse : 1) optimisation de l'équilibre charge – capacité au moyen du mode ventilatoire dit « ventilation assistée proportionnelle » (PAV), qui administre un niveau d'assistance proportionnel à l'effort inspiratoire du patient (**Chapitre 2**) ; 2) modulation de l'activité des chémorécepteurs centraux et périphériques sensibles aux variations de PaO₂, de PaCO₂ et de pH chez des patients dyspnéiques sous circulation extracorporelle (ECMO) (**Chapitre 3**) ; 3) modulation des composantes émotionnelle et sensorielle de la dyspnée par l'application de stimulations extra-respiratoires auditives et sensitives ciblées sur le cerveau (**Chapitre 4**).

Synthèse des connaissances

1. Rappel de physiologie ventilatoire

La ventilation est un acte inconscient et automatique qui participe à l'homéostasie de l'organisme en maintenant les pressions partielles tissulaires de dioxygène et de dioxyde de carbone dans des valeurs physiologiques. Elle provient de générateurs centraux du rythme respiratoire. Elle est élaborée au niveau de réseaux neuronaux localisés dans le bulbe rachidien et le pont. Cette commande est transmise via les noyaux crâniens et les motoneurones spinaux respectivement aux muscles dilatateurs des voies aériennes et aux muscles inspiratoires. Elle est modulée en permanence par des afférences respiratoires et extra – respiratoires :

- Les afférences métaboliques : issues de chémorécepteurs sensibles aux variations de PO_2 artérielle, de PCO_2 artérielle, et du pH plasmatique ou au niveau du liquide céphalo-rachidien. Ces récepteurs sont périphériques et centraux. Les premiers, situés dans les corps carotidiens sont localisés au niveau de la bifurcation des artères carotides communes ; ils sont sensibles aux variations de $PaCO_2$ et pH artériel et sont les seuls sensibles aux variations de PaO_2 . Il est observé une augmentation exponentielle de la ventilation pour une $PaO_2 < 60$ mmHg et au-delà en isocapnie ; la réponse ventilatoire dépendant du niveau préalable de $PaCO_2$ (5). Les chémorécepteurs centraux, sensibles aux variations de CO_2 et de pH du liquide céphalo-rachidien, sont situés à proximité immédiate du générateur du rythme respiratoire au niveau de la surface ventrale du bulbe rachidien dont le noyau du tractus solitaire. Cela appuie l'hypothèse d'un contrôle ventilatoire largement centré sur le métabolisme cérébral du CO_2 fournissant l'information de l'adéquation entre la ventilation alvéolaire et le métabolisme. Il est observé une forte augmentation de la ventilation pour de faibles augmentations de $PaCO_2$ (6).

- Les afférences vagales composées : a) d'afférences mécaniques, qui transmettent les informations des mécanorécepteurs de la paroi thoracique (fuseaux neuromusculaires, organes tendineux de Golgi) ; b) des mécanorécepteurs pulmonaires tels que les récepteurs pulmonaires à l'étirement (tensiorécepteurs à adaptation lente et rapide), les récepteurs à l'irritation, les fibres C amyéliniques (retrouvées dans les bronches, les alvéoles et dont les terminaisons juxta alvéolaires sont appelées récepteurs J ou « juxta-capillaires ») qui répondent à une large gamme de stimulus tels que l'hypoxie, les irritants et les toxiques (7). Les récepteurs J, situés dans l'interstitium, répondent à une augmentation du volume interstitiel pulmonaire, par exemple dans le cadre d'un œdème pulmonaire aigu cardiogénique.
- Les mécanorécepteurs des voies aériennes supérieures sensibles à l'irritation et aux modifications de pression et de débit. Les afférences de ces mécanorécepteurs sont véhiculées par les nerfs vague, glossopharyngien, grand hypoglosse et trijumeau.
- D'autres afférences provenant de récepteurs articulaires et musculaires au niveau des membres en mouvement : des barorécepteurs artériels et des afférences thermiques et nociceptives des membres.

De plus, des influx supra-pontiques peuvent modifier le contrôle ventilatoire, au cours d'états émotionnels, comme le rire, la peur ou la colère, et de tâches non volontaires comme la posture. Ainsi la modulation émotionnelle de la ventilation a été mise en évidence au cours de « locked-in » syndrome et implique le système limbique et paralimbique avec en particulier l'insula et le gyrus cingulaire (8).

Enfin, un contrôle cortical peut, dans certaines limites, interrompre le rythme automatique, permettant un contrôle volontaire de la ventilation et la réalisation d'actions telles que la phonation, la déglutition, l'apnée (9). Le cortex peut également suppléer cette commande

pour compenser une charge respiratoire, dans le cadre d'un trouble de la mécanique ventilatoire en situation pathologique ou induite expérimentalement chez un sujet sain. Lors de ces tâches, l'activation du cortex moteur et de l'aire motrice supplémentaire a été mise en évidence par électroencéphalographie et imagerie cérébrale fonctionnelle (10, 11).

2. Physiologie de la dyspnée

2.1 Neurophysiologie de la dyspnée

Il n'existe pas une mais plusieurs sensations de dyspnée (12). Ces « sensations de dyspnée » semblent sous-tendues par des mécanismes neurophysiologiques différents (3, 12-15) et peuvent coexister chez un même individu. Par exemple, la « soif d'air » décrite comme la sensation de « manquer d'air », « d'étouffer », est liée à l'hypercapnie. La sensation « d'effort excessif » ou de respiration requérant plus d'effort est rapportée à la charge mécanique imposée à l'appareil respiratoire et la « constriction thoracique » à la bronchoconstriction. En pratique clinique, ces différentes sensations sont décrites par les patients : « la soif d'air » et « l'effort excessif » chez les patients souffrant de bronchopneumopathie chronique obstructive (BPCO), « l'effort excessif » chez les patients présentant une maladie neuromusculaire et la « constriction thoracique » chez les patients asthmatiques.

Bien que les mécanismes précis de ces différentes sensations respiratoires soient mal connus, la recherche a permis d'identifier plusieurs récepteurs, voies de transmission et centres d'intégration communs ou spécifiques aux différentes sensations de dyspnée.

Ainsi, il existe plusieurs types de récepteurs impliqués dans les sensations respiratoires. Ces récepteurs sont activés par des stimulus différents et leur intégration au niveau central conduit aux différents types de sensations respiratoires, notamment :

- Les chémorécepteurs centraux et périphériques sensibles aux variations de PaO₂, de PaCO₂ et de pH ;
- Les mécanorécepteurs des voies aériennes supérieures sensibles aux variations de débits, de pression et à l'irritation ;
- Les récepteurs vagues localisés dans les voies aériennes proximales et distales, le parenchyme pulmonaire et les muscles respiratoires. Ces récepteurs intègrent des informations liées à l'étirement du parenchyme pulmonaire, à son irritation et à l'augmentation du liquide alvéolaire des cloisons interstitielles (7, 16, 17).

Parallèlement aux études chez les patients dyspnéiques, il a aussi été étudié des sujets sains rendus artificiellement dyspnéiques par différents moyens imitant les causes physiopathologiques connues de la dyspnée (18). Ainsi, une dyspnée expérimentale à type de « soif d'air » peut être provoquée chez des sujets sains grâce à la chémostimulation à réponse contrainte via deux méthodes : 1) en faisant inspirer un mélange gazeux en CO₂ tout en réduisant le volume courant de 30% (19) ; 2) en limitant l'hyperventilation réactionnelle par l'utilisation d'une ventilation mécanique contrôlée, ce qui procure une sensation de « soif d'air » stable sans solliciter excessivement l'attention des sujets ce qui peut être une source de modulation de la dyspnée.

Ces études ont permis de montrer grâce à l'imagerie par résonance magnétique fonctionnelle qu'il existe plusieurs zones cérébrales différenciellement activées selon la cause de la dyspnée (20) : le cortex moteur primaire, l'aire prémotrice D, l'aire motrice supplémentaire, le cervelet et le thalamus. Il existe deux voies afférentes principales de la dyspnée. L'une inclut le nerf vague, le tronc cérébral, le système limbique, l'insula et le cortex cingulé et est principalement associée aux composantes affectives de la dyspnée. L'autre inclut les muscles respiratoires, le tronc cérébral et le thalamus et intègre l'intensité de la dyspnée (20).

La multiplicité de ces mécanismes suggère que moduler les afférences issues de récepteurs tels que les récepteurs au froid (21), ceux de la muqueuse buccale (22) et certains mécanorécepteurs à l'étirement de la paroi thoracique (23) pourrait modifier l'intensité de la dyspnée et contribuer à la soulager.

2.2 Composantes sensorielles, émotionnelles et affectives de la dyspnée

L'une des évolutions les plus récentes et les plus marquantes dans le domaine de la physiopathologie de la dyspnée est la reconnaissance de son aspect multidimensionnel. D'un côté, il existe une composante sensorielle qui décrit la nature de la perception (« effort excessif », « soif d'air ») quantifiée en intensité et, d'un autre côté, des composantes affectives et émotionnelles décrivant ces aspects (anxiété, peur, frustration, colère, dépression...) induits par la dyspnée chez le patient, quantifiés en qualité et en intensité (caractère désagréable de la dyspnée ou « *unpleasantness* »). Physiologiquement, les composantes émotionnelles ou affectives de la dyspnée procèdent du traitement cognitivo-affectif de la sensation, et sont à la base des réactions comportementales correspondantes, à court terme et à long terme (24). Cela souligne leur importance probable dans la genèse des syndromes post-traumatiques observés après certains séjours en réanimation par exemple (4).

L'importance des facteurs psychologiques sur la perception de la dyspnée est de mieux en mieux reconnue. Plusieurs études ont montré que, comme les émotions, la mémoire, la personnalité, des expériences antérieures, pouvaient avoir un impact sur la perception de la dyspnée. En effet, chez les volontaires sains comme chez les patients souffrant d'asthme, qui présentent dans leur personnalité une émotivité négative, la dyspnée ressentie est plus intense et indépendante de l'atteinte pulmonaire sous-jacente pour les patients (25, 26).

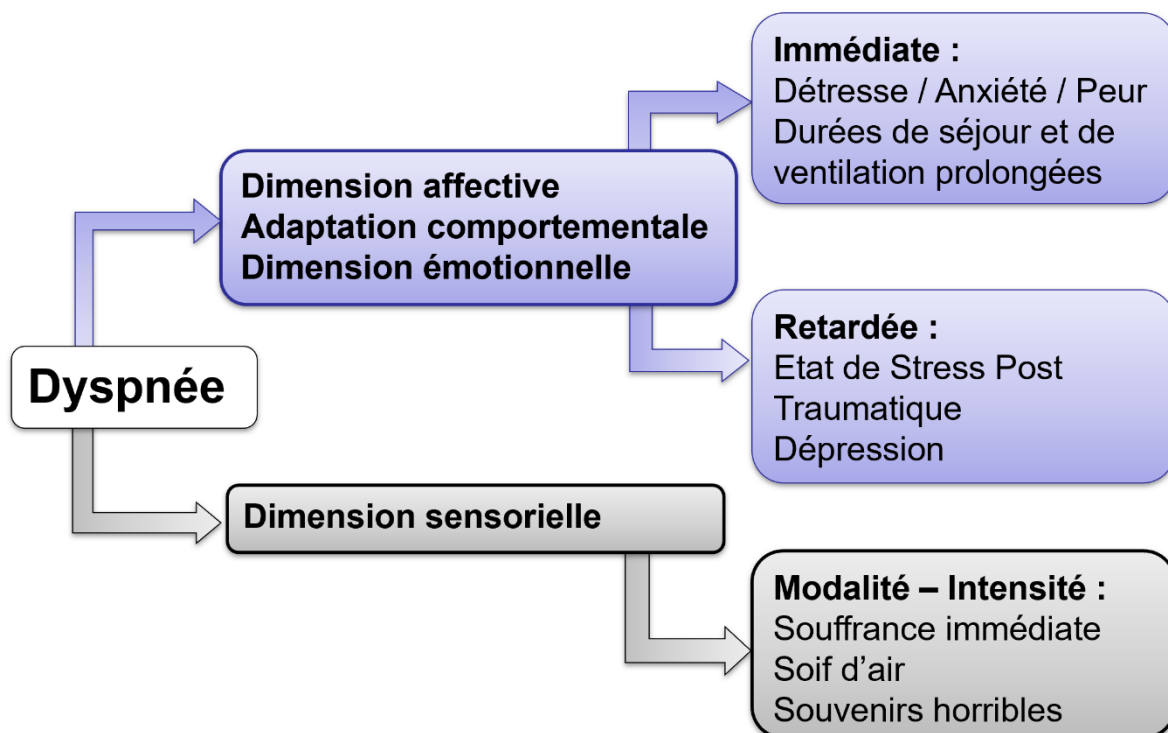


Figure 1. Composantes affectives, émotionnelles et sensorielles et leurs complications

D'après Schmidt et al., CCM, 2011 ; Demoule et al., AJRCCM, 2022 ; Cuthbertson et al. ICM, 2004 ; Pennock et al., Heart Lung, 1994 ; Rotondi et al., CCM, 2002 ; Schelling et al., Neurobiol Learn Mem, 2002 (3, 4, 27-30)

2.3 Déséquilibre entre la réponse ventilatoire souhaitée dans une situation donnée et celle réellement obtenue

L'hypothèse physiopathologique est que la dyspnée serait le résultat d'un déséquilibre entre la réponse ventilatoire souhaitée dans une situation donnée et celle réellement obtenue. Ceci repose sur le modèle neurophysiologique de prédiction motrice, selon lequel, lorsqu'une commande motrice est produite, une copie de cette commande, appelée copie d'efférence ou décharge corollaire, est également créée et projetée sur le cortex somesthésique. Dans le cas de la commande motrice respiratoire, elle constitue le projet respiratoire. La copie d'efférence est utilisée pour prédire les effets sensoriels de la commande motrice. La dyspnée apparaîtrait lors d'« incongruences » entre le projet respiratoire et les réafférences sensorielles (18). Ce phénomène aurait, comme pour la douleur, une fonction d'alarme permettant des

comportements adaptatifs ou compensatoires visant une optimisation de la ventilation efficace en termes d'échanges gazeux et la préservation d'un confort respiratoire maximal (19).

La dyspnée émane de deux niveaux d'intégration : 1) un niveau essentiellement sensorimoteur correspondant à l'intensité des sensations et relevant de la comparaison de la copie d'efférence avec les réafférences et 2) une modulation affectivo-cognitive à l'intensité de la perception désagréable ou gêne. Cette dernière est responsable d'une réponse émotionnelle immédiate (anxiété, peur, frustration, colère) et possiblement d'une réponse comportementale secondaire d'évitement impliquant les fonctions cognitives et affectives (20).

De nombreuses études d'imageries fonctionnelles chez des sujets rendus expérimentalement dyspnéiques ont mis en évidence l'activation de structures appartenant au système limbique et paralimbique, en particulier de l'amygdale, du gyrus cingulaire antérieur et de l'insula (21,22).

Ces structures sont particulièrement impliquées dans le traitement des informations viscérales et des réactions émotionnelles correspondantes, dans l'intégration des émotions et de la cognition, dans la perception consciente de la douleur (23), ainsi que d'autres sensations désagréables telles que la faim (24) et la soif (25), avec un rôle clé de l'insula antérieure et du cortex cingulaire antérieur. Ceci explique l'influence de facteurs psychologiques (émotions, cognition, attention) sur la perception dyspnéique et notamment la composante affective. Ainsi, à titre d'exemple, il est possible de moduler la perception de dyspnée en faisant visualiser aux sujets des images chargées émotionnellement, négativement ou positivement (26), en leur faisant écouter de la musique (31, 32) ou en lisant simultanément des textes (33).

Ces informations viscérales (stimulus sensoriels en lien avec l'homéostasie, tels que la faim, la soif, la douleur ou la dyspnée) dont la perception est l'intéroception, seraient perçues comme des signaux d'alarme (stimulus stressants avec impact émotionnel négatif) et permettraient un premier niveau de conscience. La conscience de soi, *i.e.* de son corps et de son

environnement, résulte de l'intégration de signaux intéroceptifs et extéroceptifs (27). La dyspnée et la perception consciente de la respiration (secondaire à des changements intéroceptifs, extéroceptifs [air froid] et proprioceptifs [position de la cage thoracique]) contribuent à cette conscience de soi et de son corps (28).

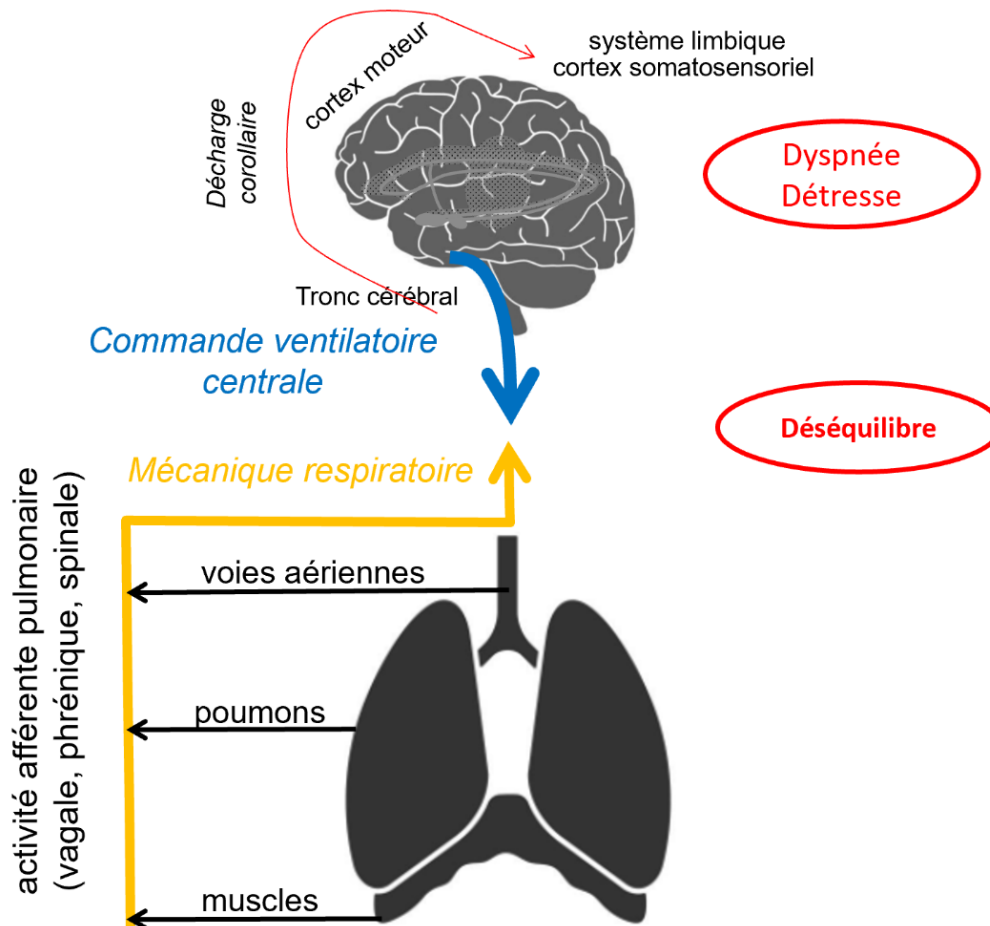


Figure 2 : Modèle neurophysiologique de la dyspnée
D'après O'Donnell DE et al., Proc Am Thorac Soc, 2007 (14)

2.4 La dyspnée comme perception d'une augmentation de l'effort respiratoire

L'effort respiratoire lui-même est principalement déterminé par les informations afférentes proprioceptives : 1) le changement de volume thoracique, 2) la tension et la force des muscles respiratoires et 3) la résistance et compliance du système thoraco-pulmonaire. La dyspnée peut naître de la perception d'une augmentation de l'effort respiratoire en cas de variations de la ventilation sous l'influence des stimulus chimiques, d'un exercice physique

(34), d'une modification de l'impédance thoraco-pulmonaire, de l'activité des muscles respiratoires (35) ou d'un changement des relations entre ces différentes variables. La dyspnée peut ainsi résulter d'un déséquilibre entre les charges imposées à l'appareil respiratoire et la capacité des muscles respiratoires à compenser les dites charges, autrement appelée « équilibre charge – capacité » (36). Ces données suggèrent que l'optimisation de l'équilibre charge – capacité pourrait soulager la dyspnée.

3. Dyspnée en réanimation : fréquence, sévérité et conséquences

Contrairement à la douleur (37), la dyspnée était un symptôme jusqu'alors peu recherché en routine en réanimation sauf lors du sevrage de la ventilation mécanique (38, 39).

Seules quelques études se sont intéressées à la prévalence et à la sévérité de la dyspnée des patients de réanimation. Ces études ont concerné principalement des patients faisant l'objet d'une ventilation mécanique. Elles montrent que la dyspnée est fréquente puisqu'elle touche entre 30 et 50% d'entre eux (3, 4, 40, 41). De plus, la fréquence de la dyspnée est inversement corrélée à un score d'humeur, qui intègre des échelles d'anxiété, de dépression, de vitalité, de fatigue et de confusion, qui témoignent de l'affect négatif associé à l'inconfort respiratoire (41). Enfin, la dyspnée en réanimation semble relativement intense, étant évaluée de modérée à sévère sur des échelles verbales par une majorité de patients (42). Dans une étude de 2011, les auteurs rapportent une médiane à 5 sur une échelle visuelle analogique (EVA) de zéro (absence de dyspnée) à 10 (pire dyspnée imaginable) (3). Une récente étude observationnelle prospective multicentrique française a porté sur 612 patients intubés. Dans cette étude, la dyspnée était mesurée dès que les patients étaient capables de communiquer, *i.e.* au premier réveil. Une dyspnée était retrouvée chez 35 % des patients et était évaluée à 50 (40-70) mm sur une EVA de zéro à 100 (4). Une cotation similaire de la douleur constituerait ainsi une indication claire et consensuelle à une analgésie rapide (43).

Tout comme celui de la douleur, l'impact immédiat de la dyspnée en tant que « souffrance » fait peu de doute, mais contrairement à la douleur, la dyspnée reflète une menace critique pour la fonction vitale (la respiration) et vaut plus que la douleur par sa dimension terrifiante, la peur de mourir. Il suffit 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 » (44, 45).

A plus long terme, la dyspnée semble 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 (41). Les patients présentant une dyspnée sans rapport avec les réglages du ventilateur sont plus tardivement sevrés que les patients non dyspnéiques (3). Comme la douleur, la dyspnée paraît donc avoir un impact sur la durée de ventilation mécanique et donc sur la durée de séjour.

Les patients survivant à un séjour en réanimation ont souvent de sinistres souvenirs de cette expérience. Le syndrome de stress post-traumatique (SSPT) est aujourd'hui une séquelle bien établie des séjours en réanimation (27). Ses facteurs de risques sont les divers facteurs anxiogènes associés à un séjour en réanimation (45, 46) et notamment le recours à l'assistance ventilatoire (47, 48). Les scores quantifiant les symptômes évocateurs de SSPT ont été décrits comme clairement corrélés aux souvenirs de détresse respiratoire et à la durée de ventilation mécanique (27). Il a été confirmé récemment dans un essai prospectif multicentrique (4) que la dyspnée est l'un des événements traumatiques participant à la genèse d'un SSPT. Dans cette étude, trois mois après la sortie de l'unité de soins intensifs, la proportion de patients présentant un probable SSPT (défini par un score ≥ 22 sur l'échelle Impact of Event Scale - Revised) était plus élevée au réveil chez les patients dyspnéiques que chez les patients non dyspnéiques.

L'incidence cumulée de la dyspnée (nombre d'épisodes de dyspnée entre l'inclusion et la fin de la ventilation mécanique) et la densité de la dyspnée (incidence cumulative de la dyspnée divisée par le nombre de jours entre l'inclusion et la fin du séjour en soins intensifs) étaient indépendamment associées à la présence d'un probable SSPT (4).

4. Soulager la dyspnée en réanimation : un état de l'art

La prise en charge de la dyspnée implique d'intégrer ses différentes composantes : la composante sensorielle qu'il faut « atténuer » et les composantes affective et émotionnelle qu'il faut « moduler ». Les sociétés savantes recommandent actuellement plusieurs approches pour soulager la dyspnée. Celles-ci impliquent des thérapies pharmacologiques et non pharmacologiques (1).

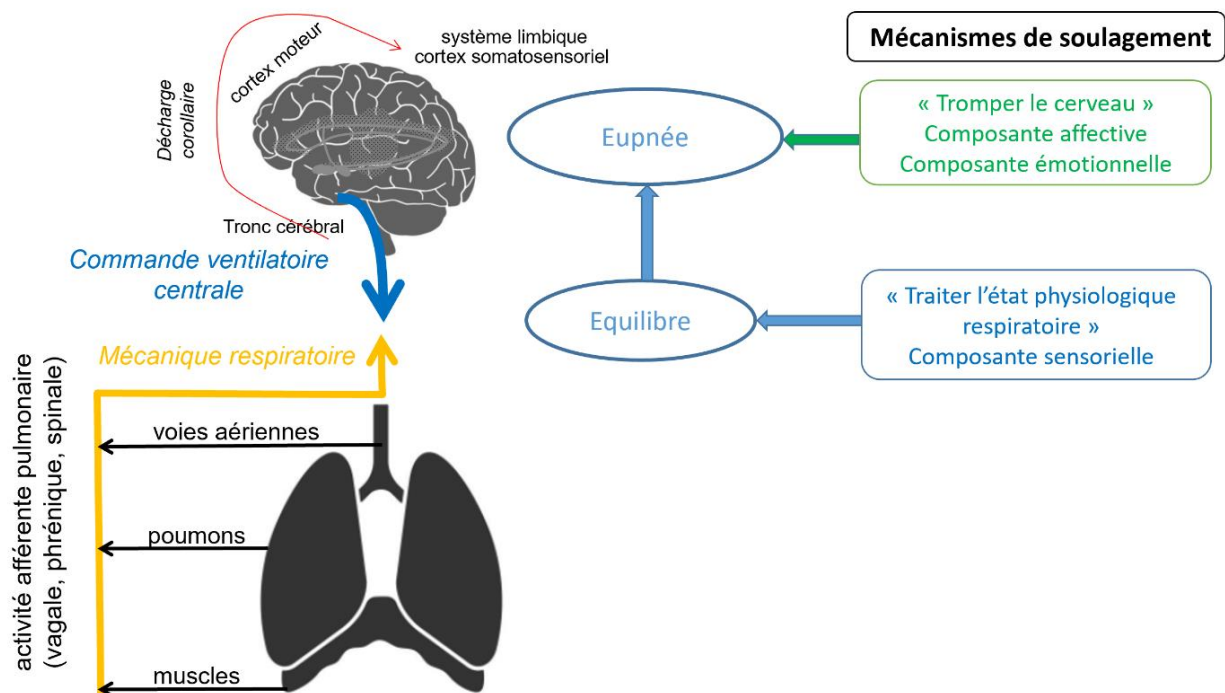


Figure 3. Modèle neurophysiologique des composantes du soulagement de la dyspnée
D'après O'Donnell DE et al., Proc Am Thorac Soc, 2007 (14)

4.1 Traitements pharmacologiques

En premier lieu, le clinicien doit s'assurer de l'optimisation des traitements spécifiques de la pathologie sous-jacente tels que les traitements bronchodilatateurs et stéroïdiens dans l'asthme, les bronchodilatateurs dans la BPCO, les diurétiques dans l'œdème pulmonaire cardiogénique.

Il existe par ailleurs des interventions pharmacologiques efficaces sur la dyspnée sans passer par un mécanisme physiopathologique étiologique. On peut classer ces traitements en deux catégories : les traitements par voie générale et les traitements inhalés.

Concernant les traitements par voie générale, les opioïdes sont actuellement les molécules les plus administrées ; utilisant des voies nerveuses communes avec la douleur (49). Leur efficacité à soulager la dyspnée à court terme est bien étudiée et démontrée (15, 50). Leur efficacité à plus long terme n'est en revanche pas prouvée et leurs effets indésirables, notamment leur effet dépresseur respiratoire, doivent être pris en compte lors de leur prescription. Les autres traitements médicamenteux tels que les anxiolytiques, les antidépresseurs et les anti-inflammatoires n'ont pas démontré d'efficacité sur la dyspnée (51, 52).

Pour ce qui est des thérapeutiques inhalées, le furosémide a montré un effet sur la dyspnée chez des patients souffrant d'asthme ou de BPCO (53) mais pas chez les patients atteints de cancers du poumon (54). Les anesthésiques inhalés n'ont pas démontré d'efficacité sur la dyspnée (55). Enfin, même la place de l'oxygénothérapie dans le traitement de la dyspnée est débattue : il est montré que l'oxygène améliore la qualité de vie et diminue la mortalité des patients mais sa capacité à soulager la dyspnée n'est pas prouvée (56, 57). L'hélium n'a montré son bénéfice que dans une seule étude (58).

4.2 Traitements non pharmacologiques

Plusieurs thérapies non médicamenteuses ont été évaluées chez des patients présentant une dyspnée. Ces thérapeutiques font actuellement partie du domaine de la recherche. Les médecines parallèles comme l'acupuncture (59, 60) et les techniques de relaxation (61) n'ont pas pour l'instant montré de bénéfice sur la dyspnée. Elles ont fait l'objet d'études peu nombreuses portant sur un petit nombre de patients.

Induire des vibrations au niveau de la cage thoracique chez les patients porteurs de BPCO soulage la dyspnée (62, 63). Le site d'application des vibrations est variable d'un patient à l'autre dans la littérature et il n'existe pas d'appareil commercialisé pouvant induire ces vibrations. Plusieurs études ont montré que l'administration d'air frais au niveau du visage pouvait induire une diminution de l'intensité de la dyspnée (21, 64). Il n'existe pas à ce jour de grand essai clinique randomisé. Ces thérapies non pharmacologiques ont pour point commun de distraire l'attention du sujet. Dans la mesure où la pharmacopée à disposition du clinicien pour soulager la dyspnée est restreinte, et où les effets indésirables de cette pharmacopée peuvent avoir un impact négatif (dépression ventilatoire), le développement de techniques visant à moduler de façon sensorielle et émotionnelle la dyspnée représente une alternative thérapeutique intéressante.

4.3 Rôle de la ventilation mécanique dans la genèse de la dyspnée

Alors que la ventilation mécanique a pour objectif principal de suppléer tout ou une partie de la fonction respiratoire lorsque l'appareil respiratoire est défaillant, elle est paradoxalement bien souvent une source de dyspnée et d'inconfort. Toutefois, il s'agit d'une cause réversible de dyspnée. En effet, chez 35% des patients ventilés présentant une dyspnée, une simple optimisation des réglages du ventilateur permet de diminuer de façon importante l'intensité de cette dyspnée (3).

Les réglages du ventilateur qu'il est possible de modifier de façon à diminuer la prévalence et la sévérité de la dyspnée sont les suivants :

- Le mode ventilatoire : le mode assisté-contrôlé, plus contraignant pour l'appareil respiratoire, est associé à plus de dyspnée (65). Le débit inspiratoire, lorsqu'il est trop faible, induit une augmentation de la dyspnée (66, 67). Il en va de même du temps de pressurisation ou pente inspiratoire (68, 69);
- Le volume courant : insuffisant, il induit une « soif d'air » (70-72);
- Le niveau d'assistance : les niveaux d'aide inspiratoire particulièrement faibles (< 10 cmH₂O) ou au contraire beaucoup trop élevés (> 25 cmH₂O) sont associés à la survenue d'une dyspnée (73).

4.4 Soulager la dyspnée en réanimation

Bien que l'évaluation de la dyspnée ne soit pour l'instant possible que chez des patients de réanimation communicants, puisque l'objectiver et la quantifier nécessitent la participation du patient ou le recours à des échelles d'hétéroévaluation, il n'est aujourd'hui plus envisageable d'ignorer ce symptôme fréquent et intense chez les patients sous ventilation mécanique. Chez ces patients, l'optimisation de la ventilation mécanique n'est pas suffisante à elle seule pour soulager la dyspnée (3). De plus, l'utilisation prolongée de morphiniques est associée, outre ses effets indésirables habituels, à une augmentation de la durée de sevrage de la ventilation mécanique (74). D'autres outils thérapeutiques doivent absolument être étudiés afin d'améliorer la prise en charge de ces patients, non seulement en termes de confort mais également dans l'objectif d'éviter le sevrage prolongé de la ventilation mécanique.

5. Soulager la dyspnée en réanimation : perspectives et objets d'étude

Soulager la dyspnée pour améliorer le confort immédiat des patients en réanimation et réduire la prévalence de certaines séquelles comme les syndromes de stress post traumatique représentent un objectif thérapeutique majeur. En réanimation, l'utilisation des traitements pharmacologiques de la dyspnée se heurte à la complexité de leur utilisation et à leurs effets indésirables. De plus, l'optimisation des réglages du ventilateur ne soulage la dyspnée que chez un tiers des patients (3, 75). Au cours des dernières années, la façon de ventiler les patients a également évolué et l'objectif n'est plus seulement de les assister mais de ne pas leur nuire. Ainsi, la ventilation protectrice des poumons qui est recommandée (76) s'accompagne d'une sous-assistance qui expose les patients à une dyspnée, en particulier lorsque le volume courant est faible (71). Ainsi, le soulagement de la dyspnée par l'augmentation du volume courant est limité par le risque de volotraumatisme. Lorsqu'une décision est prise de soulager la dyspnée chez les patients sous ventilation mécanique, un équilibre entre le soulagement de la dyspnée et les effets potentiellement délétères d'une sur-assistance ventilatoire doit être envisagé. Enfin, en l'absence des propriétés physiologiques de l'appareil respiratoire, définies par ses propriétés mécaniques (résistance et élastance) ainsi que celles de la barrière alvéolocapillaire, il est souvent difficile de trouver un traitement étiologique et, dans un certain nombre de cas, ce traitement ne suffit pas. Les moyens de prise en charge de la dyspnée connaissent donc des limites, raison pour laquelle il est important d'étudier de nouvelles pistes thérapeutiques.

5.1 Ventilation assistée proportionnelle

5.1.1 Limites du mode ventilation spontanée avec aide inspiratoire

Les modes de ventilation dits « partiels » regroupent l'ensemble des modes ventilatoires autorisant une participation du patient à la genèse du volume courant. Par le maintien d'une activité respiratoire spontanée et la possibilité d'une meilleure adéquation avec l'activité de la

commande respiratoire centrale, les modes de support partiel participent à la prévention de la dysfonction diaphragmatique liée à la ventilation mécanique (77-79), au recrutement pulmonaire (80), à la réduction des asynchronies patient-ventilateur (81) et de l'utilisation de sédatifs, pouvant permettre *in fine* l'accélération du processus de sevrage ventilatoire (82).

L'utilisation de la ventilation en mode partiel doit toutefois tenir compte d'une contrainte majeure : assurer une adéquation satisfaisante entre les efforts inspiratoires et 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'une des principales limites des modes de ventilation assistés conventionnels tels que la ventilation spontanée avec aide inspiratoire (VSAI) est que la pression d'assistance reste constante, quel que soit l'effort inspiratoire développé par le patient. Il peut donc en résulter une inadéquation entre une demande élevée du patient et une offre insuffisante par le ventilateur, laquelle conduit à la genèse d'une dyspnée et d'asynchronies telles que les doubles déclenchements. Si au contraire la demande est inférieure à l'offre, il apparaît une surdistension conduisant à la survenue d'appels inefficaces. L'optimisation des réglages du ventilateur permet, certes, de limiter cette dysharmonie entre le patient et le ventilateur, toutefois, cela nécessite des interventions fréquentes et chronophages qui ne sont pas compatibles avec l'exercice clinique. C'est dans le but de contourner cette limite de la VSAI qu'ont été développés les modes proportionnels.

5.1.2 Principe de fonctionnement de la ventilation assistée proportionnelle

Les modes proportionnels reposent sur la proportionnalité de l'assistance délivrée par le ventilateur à l'effort inspiratoire du patient. 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 commande ventilatoire qui surviennent au cours du temps.

En agissant au plus proche de la commande ventilatoire du malade, ces modes proportionnels s'affranchissent d'un des principaux écueils de la VSAI qui est de supposer que la demande ventilatoire reste stable au cours du temps délivrant ainsi une assistance fixe.

Les modes proportionnels devraient théoriquement apporter une réponse aux problèmes posés par les modes conventionnels tels que la sur-assistance, la sous-assistance et les asynchronies patient-ventilateur ainsi que la dyspnée qui en résulte (81-87). La PAV est l'un des principaux modes proportionnels actuellement disponibles.

Son principe est en grande partie fondé sur l'équation du mouvement du système respiratoire. La mesure des débits et des volumes instantanés produits par le patient permet d'estimer son effort musculaire. Ceci nécessite la mesure de l'élastance et de la résistance de l'appareil respiratoire ; cette mesure 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 (88, 89). De cette façon, 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 (90, 91). En pratique, le réglage du ventilateur ne s'effectue pas sur cette constante de proportionnalité mais sur un « gain » qui représente le pourcentage de la pression totale appliquée pris en charge par le ventilateur et contenu dans le rapport de proportionnalité. Ainsi, pour un réglage du ventilateur donné, la PAV s'adaptera automatiquement aux variations de charge ou de demande ventilatoire (92-95). En 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.

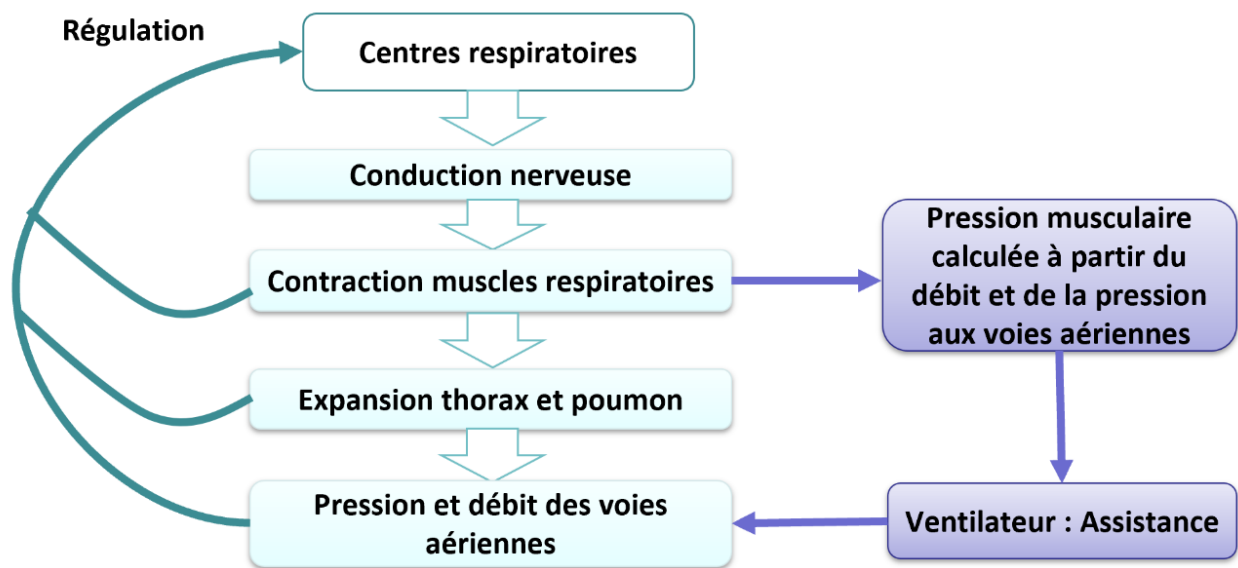


Figure 4 : Mode de fonctionnement de la ventilation assistée proportionnelle

5.1.3 Bénéfices du mode PAV

Plusieurs études se sont intéressées à l'impact physiologique de la PAV et en ont constaté plusieurs bénéfices. Premièrement, la PAV prévient la surdistension thoracique. En effet, la PAV étant asservie à l'effort inspiratoire du patient, une augmentation du niveau d'assistance entraînera une diminution de l'effort inspiratoire sans effet ou presque sur le volume courant (86). Deuxièmement, en limitant le risque de distension dynamique, la PAV prévient la survenue d'appels inefficaces et améliore donc la synchronie patient – ventilateur (83, 96-98). Troisièmement, la PAV restaure la variabilité naturelle de la ventilation en s'adaptant à la commande respiratoire propre du patient sans lui imposer une assistance fixe comme en VSAI (89, 92-95). Quatrièmement, la PAV pourrait améliorer le confort respiratoire (99-102).

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 plus souvent et réduisait ainsi les retours en mode contrôlé (98). Une seconde étude, plus récente, a montré qu'il était possible

de maintenir en PAV des patients dans une zone de confort pendant une période prolongée de plusieurs jours (103). En revanche, aucun essai n'a montré une supériorité de la PAV sur la VSAI avec comme critères la mortalité ou le taux d'intubation.

5.1.4 Intérêt potentiel de la PAV dans la prise en charge de la dyspnée en réanimation

Plusieurs éléments suggèrent que la PAV pourrait soulager la dyspnée et plaident pour une évaluation de ce mode chez des patients dyspnéiques. Tout d'abord, la PAV adaptant l'offre du ventilateur à la demande du patient, il est légitime de faire l'hypothèse qu'elle améliore l'équilibre charge capacité et donc réduit l'intensité de la commande centrale, la dyspnée et les asynchronies. Les données montrant que la PAV diminue la surdistention thoracique (86) et donc les appels inefficaces (83, 96-98) sont en faveur de cette hypothèse. Des données physiologiques préliminaires suggèrent que le confort respiratoire pourrait être meilleur en PAV (104).

Parce que la PAV délivre un niveau d'assistance plus adaptée à l'effort inspiratoire que ne le fait la VSAI, la PAV pourrait améliorer de façon plus marquée l'adéquation entre charge et commande centrale. Par conséquent, la PAV pourrait soulager la dyspnée de façon plus efficace que la VSAI.

5.2 Modulations sensorielles, émotionnelles et affectives de la dyspnée

Moduler la dyspnée par des processus attentionnels est une perspective thérapeutique séduisante. On peut en effet supposer que lorsque l'on détourne la vigilance du sujet vers un autre stimulus, on peut « tromper le cerveau » et ainsi réduire la perception de la sensation de dyspnée en termes d'intensité et/ou d'affect ; et ce sans modification de l'état physiologique respiratoire par un traitement étiologique ou pharmacologique, et par conséquent sans modulation de la commande centrale. Ainsi, en modulant les composantes émotionnelles et affectives et sans influencer l'équilibre entre la commande centrale respiratoire et les afférences

périphériques, on pourrait obtenir un soulagement de la dyspnée. Des données similaires existent pour la douleur. Il a par exemple été constaté que des patients recevant des soins dentaires ressentait moins la douleur lorsqu'ils regardent un film simultanément (105).

5.2.1 Modulation sensorielle

Plusieurs travaux ont évalué l'effet de distractions sensorielles sur la dyspnée chez le volontaire sain et chez les patients. L'administration d'air frais au niveau du visage chez le volontaire sain réduit l'intensité de la dyspnée induite par une charge résistive (21, 64) en stimulant le nerf trijumeau et ainsi en provoquant une compétition sensorielle par le phénomène du *gating*. Cet effet n'est pas retrouvé lorsque l'air est appliqué sur le mollet (21). Chez des patients de soins palliatifs souffrant de dyspnée réfractaire, l'administration d'air dirigée vers le visage à l'aide d'un ventilateur s'associe à une diminution de 30% de l'intensité de la dyspnée (64).

5.2.2 Modulations affectives et émotionnelles

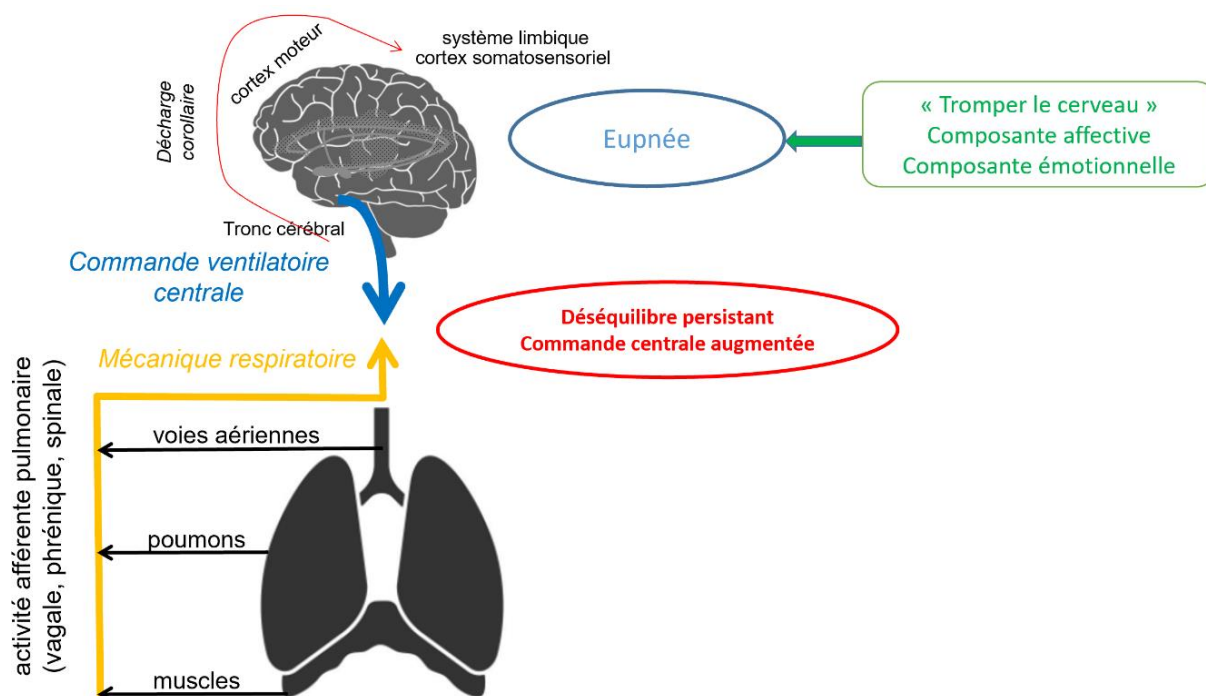


Figure 5. Le soulagement de la dyspnée via les composantes affectives et émotionnelles
D'après O'Donnell DE et al., Proc Am Thorac Soc, 2007 (14)

Les composantes affectives et émotionnelles de la dyspnée étant le reflet d'un traitement cognitif, il est possible de les moduler en induisant des émotions.

Plusieurs travaux ont évalué l'effet de distractions diverses sur la dyspnée, chez le volontaire sain et chez les patients. L'écoute d'une pièce musicale de leur choix réduit la dyspnée chez des patients souffrant de BPCO (106). Une étude a établi que ce n'était pas l'intensité mais la composante affective de la dyspnée qui s'améliorait sous l'effet d'un stimulus auditif distrayant (32). Des études ont même constaté une amélioration significative des performances des patients au test de marche de 6 minutes (31, 32) ainsi qu'une diminution de l'intensité de la dyspnée à l'exercice (31). D'autres distracteurs ont été évalués. Ainsi la composante affective était réduite chez le volontaire sain, soumis à une dyspnée expérimentale de type effort excessif, à qui l'on demandait de lire des textes en même temps que l'induction de la dyspnée (33).

Lorsque l'on fait défiler des images à connotations positives, neutres et négatives devant un volontaire sain, il est observé une augmentation du niveau de la composante affective de la dyspnée lorsque les images suggèrent des émotions négatives (107, 108). Chez les patients asthmatiques (107) ou souffrant de BPCO soumis à un exercice physique, les symptômes relatifs à la dyspnée augmentent également lorsqu'on leur présente des images négatives. A l'inverse, chez les enfants asthmatiques, la perception de la dyspnée diminue lorsqu'on leur montre un film joyeux (109).

5.2.3 Modulation de la dyspnée en réanimation

La perception de la dyspnée est corrélée à l'anxiété des patients (110). Or, il n'existe pas d'études évaluant la modulation sensorielle et affective de la dyspnée chez les patients de réanimation. En revanche, plusieurs travaux font état d'un effet positif de la musique chez le patient de réanimation sur l'amélioration de la qualité du sommeil (111), la diminution de

l'anxiété globale (112), et lors de l'épreuve de sevrage de la ventilation mécanique (113). Cette diminution de l'anxiété s'accompagne d'une diminution de la fréquence respiratoire (113). En revanche, dans une étude réalisée chez des patients sous ventilation non invasive pour une insuffisance respiratoire aiguë, une intervention musicale ne diminuait pas l'inconfort respiratoire (114).

Les travaux réalisés chez les volontaires sains et les patients insuffisants respiratoires chroniques suggèrent que des modulations sensorielle et affectivo-émotionnelle de la dyspnée pourraient permettre de soulager cette dernière de façon au moins équivalente à un ajustement des réglages du ventilateur, sans pour autant affecter l'intensité de la commande ventilatoire centrale.

5.3 Circulation extra-corporelle (ECMO)

5.3.1 Circulation extra-corporelle : indications et principe de fonctionnement

L'ECMO veino-artérielle (ECMOva) est une circulation extracorporelle qui supplée aux fonctions cardiaques et circulatoires. Elle est indiquée lorsqu'il existe une défaillance cardiocirculatoire sévère. Il peut s'agir d'affections pour lesquelles l'assistance est placée dans l'attente d'une récupération fonctionnelle spontanée : c'est le cas des myocardites ou du choc cardiogénique réfractaire des cardiotoxiques. Dans d'autres cas, l'assistance circulatoire est implantée dans l'attente d'un diagnostic, d'une chirurgie de réparation ou d'une transplantation cardiaque (115, 116).

Un circuit d'ECMOva est constitué de deux canules, une d'admission veineuse et une de réinjection artérielle, d'une pompe centrifuge et d'une membrane ou « oxygénateur » permettant les échanges gazeux (Figure 6a). Le sang circule dans la membrane et le mélange gazeux est injecté dans les capillaires de la membrane. Ainsi, le sang qui revient au patient est à la fois oxygéné et décarboxylé. L'oxygénation dépend de la FiO_2 réglée (de 21 à 100 % selon

les besoins) et la décarboxylation dépend du débit de gaz injecté dans la membrane, autrement appelé « balayage », qui varie de 0 L/min à 10 L/min (Figure 6b). Donc, même si l'ECMOva a pour objectif principal d'assurer une suppléance cardio-circulatoire, elle implique également une assistance respiratoire.



Figure 6 : Circulation extra-corporelle : oxygénateur (a) et balayage (b)

5.3.2 Circulation extra-corporelle et dyspnée

Une dyspnée est communément observée chez les patients sous ECMOva, alors même que l'hématose est parfaitement assurée par l'ECMOva. Plusieurs mécanismes peuvent expliquer cette dyspnée.

Le premier mécanisme est la stimulation des récepteurs J par l'œdème pulmonaire hémodynamique. L'œdème pulmonaire hémodynamique résulte du fait que, sous ECMOva, le court-circuit cœur-poumon n'est pas total et qu'une partie du sang veineux transite encore par la circulation pulmonaire. En conséquence, lorsque l'activité cardiaque est absente ou faible, incapable d'ouvrir les valves aortiques, et ce d'autant qu'un flux sanguin rétrograde provenant de l'ECMO vient en sens inverse, peut alors survenir une stase sanguine dans le ventricule gauche. Cette stase est responsable d'une dilatation de l'anneau mitral et d'une insuffisance mitrale, à l'origine d'un œdème pulmonaire hémodynamique parfois massif.

Le second mécanisme est l'hypercapnie, potentiellement causée par un débit de balayage insuffisant de la membrane d'ECMO. En effet, le débit de balayage de la membrane conditionne l'épuration du CO₂ du circuit d'ECMO, la diminution du dit balayage diminue l'épuration du CO₂ et s'accompagne donc d'une augmentation de la PaCO₂. Par conséquent, chez un patient sous ECMO présentant une dyspnée, l'un des moyens de diminuer cette dyspnée serait de moduler l'activité des chémorécepteurs en augmentant le débit de balayage.

Au total, il n'est pas inhabituel de constater une dyspnée chez les patients sous ECMOva, laquelle constitue un modèle unique d'étude de la dyspnée via une modulation des chémorécepteurs centraux et périphériques sensibles aux variations de PaCO₂ et de pH, par des balayages de la membrane d'ECMO de débit variable.

Position du problème et hypothèses

En réanimation, la moitié des patients sous ventilation artificielle ressentent une dyspnée dont l'intensité est modérée à sévère. Cette dyspnée a un impact négatif sur la durée de ventilation mécanique, sur le confort des patients et sur l'incidence du SSPT.

Toutes les raisons précédemment énoncées ne permettent plus aujourd'hui d'ignorer ni de minimiser la dyspnée des patients sous ventilation mécanique. En effet, l'optimisation de la ventilation artificielle ne permet de soulager la dyspnée que chez une partie de ces patients, alors même que les stratégies de ventilation protectrices des poumons et du diaphragme et d'épargne de médicaments sédatifs limitent la possibilité d'augmenter le volume courant. De plus, l'utilisation prolongée de morphiniques, actifs sur la dyspnée, est associée à une augmentation de la durée de sevrage de la ventilation mécanique (74), en plus de ses effets indésirables habituels (hypoventilation, constipation, nausées), rendant leur emploi difficile chez des patients en état critique. Enfin, traiter l'étiologie de la dyspnée d'un appareil respiratoire dont les propriétés physiologiques sont altérées n'est pas toujours possible et souvent long.

D'autres outils thérapeutiques doivent être étudiés dans l'objectif de soulager la dyspnée et donc d'améliorer la prise en charge de ces patients, non seulement en termes de confort, mais également afin de réduire la durée du sevrage de la ventilation mécanique et la survenue des complications neuropsychologiques de la réanimation.

La prise en charge de la dyspnée repose sur l'intégration des deux composantes : 1) la composante sensorielle qu'il faut « atténuer », 2) les composantes émotionnelles et affectives qu'il faut « moduler ». Les sociétés savantes recommandent plusieurs approches non pharmacologiques pour la prise en charge de la dyspnée (1). Ainsi, les patients souffrant de BPCO peuvent bénéficier de stimulations électriques musculaires et de vibrations induites au

niveau de la cage thoracique (117). De même, chez les patients en soins palliatifs, l'hypnose et les techniques de relaxation ont démontré un bénéfice (118).

La première hypothèse de ce travail est que, chez des patients de réanimation sous ventilation mécanique, l'intensité de la dyspnée est plus fortement liée à l'activité électromyographique des muscles inspiratoires extradiaphragmatiques qu'à l'activité électromyographique du diaphragme. Nous avons testé cette hypothèse au cours de l'épreuve de ventilation spontanée permettant d'évaluer la possibilité de libérer le patient du ventilateur, cette épreuve étant particulièrement susceptible d'induire une dyspnée.

Nous faisons ensuite trois hypothèses concernant des cibles potentielles permettant de soulager la dyspnée chez les patients ventilés en « atténuant » la composante sensorielle et en « modulant » les composantes affectives et émotionnelles.

- 1) En adaptant l'offre du ventilateur à l'effort inspiratoire et donc la commande ventilatoire du patient, le mode PAV devrait théoriquement diminuer l'intensité de la dyspnée observée par rapport aux modes conventionnels.
- 2) La perception de la dyspnée semble être fortement soumise aux processus attentionnels et émotionnels des patients. Agir sur le traitement de l'information cognitive via une stimulation sensorielle ou auditive pour moduler la perception de la dyspnée devrait soulager ce symptôme. Sa simplicité de réalisation et son innocuité en comparaison de traitements pharmacologiques méritent d'être soulignées.
- 3) L'ECMOva offre un modèle d'étude des mécanismes impliqués dans le soulagement de la dyspnée en permettant de faire varier le balayage de la membrane, ce qui devrait permettre de diminuer l'intensité de la commande ventilatoire centrale ainsi que l'intensité de la dyspnée en modulant la PaCO₂.

Objectifs

Le premier objectif de ce travail est donc de déterminer si l'intensité de la dyspnée, marqueur de l'intensité de la commande respiratoire centrale et donc indirectement de l'équilibre charge – capacité est plus fortement liée à l'activité électromyographique du diaphragme ou à celle des muscles inspiratoires extradiaphragmatiques.

Les trois objectifs suivants sont d'étudier l'impact sur la dyspnée de trois interventions modifiant les processus d'intégration impliqués dans sa genèse :

- 1) L'optimisation de l'équilibre charge – capacité au moyen du mode ventilatoire PAV qui administre un niveau d'assistance proportionnel à l'effort inspiratoire du patient.
- 2) La modulation des composantes émotionnelles, affectives et sensorielles de la dyspnée par l'application de stimulations extra-respiratoires auditives (musique relaxante) et sensitives (flux d'air sur le visage).
- 3) La modulation des chémorécepteurs centraux et périphériques sensibles aux variations de PaCO₂ et de pH chez des patients dyspnéiques sous ECMOva.

Méthodes d'exploration de la dyspnée et de la commande centrale respiratoire

1. Exploration de la dyspnée

Il existe plusieurs outils pour évaluer l'intensité ainsi que les caractéristiques sensorielles et affectives de la dyspnée.

1.1 Mesures psychophysiques

En routine, la mesure la plus simple à utiliser est une échelle ordinale, graduée de 0 (absence de dyspnée) à 10 (pire dyspnée imaginable) mesurant l'intensité ou une échelle catégorielle permettant à l'aide d'un champ sémantique de caractériser la dyspnée. L'EVA (119) est l'échelle analogique de référence. L'EVA permet d'évaluer la composante sensorielle de la dyspnée représentée par une ligne visuelle de 10 cm entre deux extrémités : 0 « sensation nulle » / « aucune gêne » et 10 « sensation maximale » / « gêne insupportable ». L'EVA ne prend cependant en compte qu'une seule dimension de la dyspnée qui n'est pas toujours clairement identifiée et qui peut changer selon l'intensité rapportée de l'inconfort respiratoire.

L'échelle de Borg (119) est une échelle catégorielle, validée pour les patients atteints de pathologies neuromusculaires ou bronchiques, qui évalue uniquement la dimension sensorielle en guidant le patient au moyen d'une catégorisation sémantique, allant de « rien du tout » à maximum ».

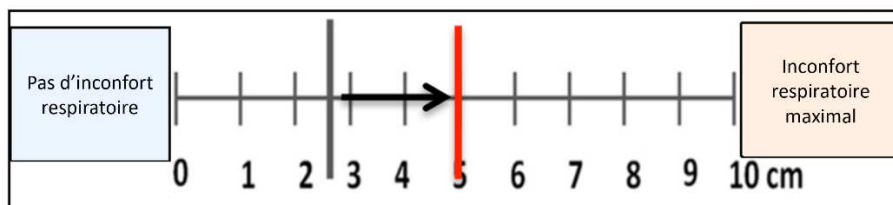


Figure 7 : Échelle visuelle analogique de dyspnée

1.2 Mesures psychosensorielles

Afin de prendre en compte l'aspect multidimensionnel de la dyspnée, de nouveaux questionnaires ont été développés. Le Multidimensionnal Dyspnea Profile (MDP) (120) est inspiré des échelles d'évaluation de la douleur et possède une très bonne reproductibilité. Ce questionnaire distingue une composante affective immédiate qui quantifie l'inconfort respiratoire, une composante sensorielle qui décrit la nature de la perception (« effort excessif », « soif d'air », « constriction thoracique », « effort mental ») et enfin la réponse émotionnelle qui en découle (anxiété, peur, frustration, colère, dépression...) (121).

Il est constitué comme suit :

- La dimension sensorielle A1 évalue l'inconfort respiratoire grâce à une échelle ordinale allant de 0 (pas de gêne respiratoire) à 10 (gêne respiratoire insupportable).
- La dimension sensorielle et la réponse émotionnelle sont évaluées en utilisant également une échelle ordinale de 0 à 10 pour chaque item ; 0 correspondant à l'absence de la sensation/sentiment et 10 correspondant à la plus forte intensité imaginable. Il y a cinq caractères sensoriels (SQ1, besoin de fournir un effort ou un travail pour respirer ; SQ2, manque d'air, étouffement ou besoin d'air ; SQ3, serrement ou compression thoracique ; SQ4, effort mental pour respirer ; SQ5, respiration forte) et cinq sentiments (E1, déprimé ; E2, anxieux ; E3, frustré ; E4, en colère ; E5, effrayé).

A partir de ces trois dimensions, deux scores sont calculés :

- Le score perceptuel est calculé en additionnant les scores A1 et SQ1 à SQ5 (score maximal de 60).
- Le score émotionnel est calculé en additionnant les scores E1 à E5 (score maximal de 50).

Ces scores sont longs à réaliser et difficiles à utiliser en réanimation, notamment chez les patients intubés sous ventilation mécanique avec lesquels la communication est complexe et une version simplifiée est souvent nécessaire (122).

A. ECHELLE A1 - AFFECT

NI AGRABLE NI GENANT	0	1	2	3	4	5	6	7	8	9	10	INSUPPORTABLE
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B. ECHELLE A2 – AFFECT

	JE N'ÉPROUVE PAS CE SENTIMENT										J'ÉPROUVE CE SENTIMENT DE LA PIRE FACON IMAGINABLE											
Déprimé(e)	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
Anxieux(se)	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
Frustré(e)	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
En colère	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
Effrayé(e)	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10

C. CHOIX QS – QUALIFICATEUR SENSORIEL

	ETAPE 1		ETAPE 2
	Ne s'applique pas	S'applique	S'applique le mieux
Je dois fournir un travail ou un effort musculaire pour respirer.			
Je manque d'air ou j'étouffe ou je sens que j'ai besoin d'air.			
J'ai la sensation que ma poitrine et mes poumons sont serrés ou comprimés.			
Je dois me concentrer ou faire un effort mental pour respirer.			
Je respire fort.			

D. ECHELLE QS – QUALIFICATEUR SENSORIEL

	JE N'ÉPROUVE PAS CETTE SENSATION										LA PLUS FORTE INTENSITE											
Je dois fournir un travail ou un effort musculaire pour respirer.	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
Je manque d'air ou j'étouffe ou je sens que j'ai besoin d'air.	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
J'ai la sensation que ma poitrine et mes poumons sont serrés ou comprimés.	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
Je dois me concentrer ou faire un effort mental pour respirer.	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
Je respire fort.	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10

Figure 8 : Multidimensionnal Dyspnea Profile
D'après Banzett et al., Eur Respir J., 2015 (120)

1.3 Échelles d'hétéroévaluation de la dyspnée

Parce que les patients de réanimation ne peuvent souvent pas communiquer, des échelles d'hétéroévaluation ont été développées afin d'évaluer la présence d'une dyspnée en se basant sur l'observation du patient.

La première de ces échelles à avoir été développée est le score RDOS (Respiratory Distress Observation Scale) d'évaluation de la dyspnée (123, 124). Décrit en milieu de soins palliatifs, il évalue la présence d'une dyspnée à partir de signes respiratoires (polypnée, utilisation des muscles du cou, respiration abdominale paradoxale, battement des ailes du nez), de réactions végétatives associées à la dyspnée (tachycardie), et de réactions émotionnelles (expression faciale de peur et degré d'agitation). Un score supérieur à 6 permet de prédire une EVA supérieure à 4.

Le score d'hétéroévaluation IC-RDOS (Intensive Care - Respiratory Distress Observation Scale) a été développé plus récemment et est plus spécifiquement adapté aux

patients de réanimation (122, 125). Cette échelle a été conçue pour identifier la « souffrance respiratoire occulte » (126) chez les patients de réanimation, qui ne peuvent souvent pas signaler eux-mêmes leur dyspnée (127) et chez qui les soignants ont des difficultés à l'identifier (128, 129). Il s'agit d'une échelle en cinq points qui prend en compte le besoin d'oxygène, la fréquence cardiaque, l'utilisation des muscles du cou, la respiration abdominale paradoxale pendant l'inspiration, et l'expression faciale de la peur (130). Un IC-RDOS à 2,4 prédit une EVA supérieure ou égale à 4 avec une sensibilité et une spécificité identique de 72%. Un IC-RDOS à 6,3 prédit une EVA supérieure ou égale à 4 avec une spécificité de 100 % (130).

2. Mesure de l'intensité de la commande centrale respiratoire

2.1 Électromyogramme (EMG) des muscles inspiratoires

L'amplitude de l'activité EMG des muscles inspiratoires extradiaphragmatiques est proportionnelle à l'intensité de la dyspnée et traduit l'intensité de la commande respiratoire centrale (131). L'activité de plusieurs muscles peut être recueillie : muscles scalènes, muscles intercostaux parasternaux (en regard du 2^{ème} espace intercostal, au plus près du sternum), muscles *Alae Nasi* (sur les ailes du nez). Ces signaux sont recueillis au moyen d'électrodes de surface. Toutefois, le rapport signal/bruit de l'activité EMG phasique des muscles du cou recueillie par les électrodes de surface est faible. En revanche, le moyennage du signal EMG à la surface des scalènes permet d'optimiser le rapport signal/bruit (132). Cette méthode peut être appliquée à d'autres muscles inspiratoires extradiaphragmatiques tels que les muscles intercostaux parasternaux (133) ou les ailes du nez (134).

L'EMG du diaphragme est obtenu à partir du cathéter nasogastrique multi-électrodes NAVA (Neurally Adjusted Ventilatory Assist), une sonde œsophagienne qui recueille le signal EMG avec des électrodes bipolaires dans un ordre séquentiel. Sa proportionnalité à l'intensité de la dyspnée est moins claire.

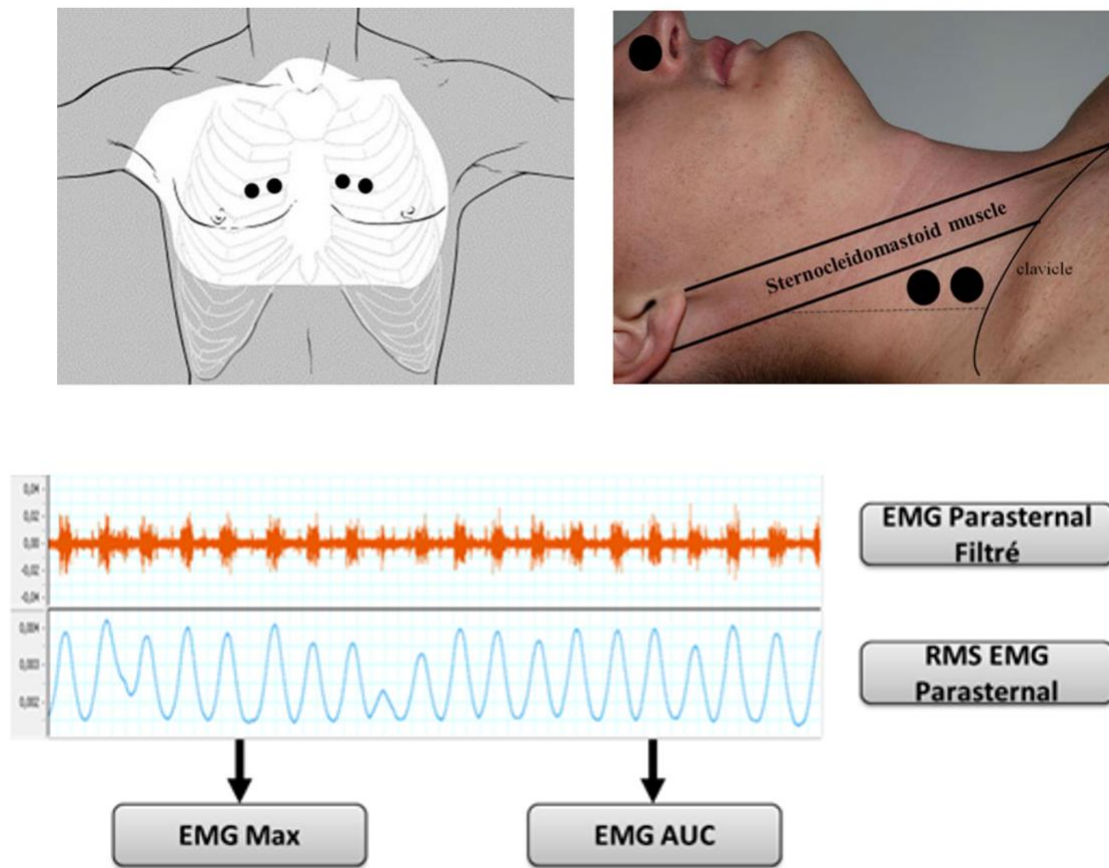


Figure 9 : Electromyographie des muscles inspiratoires extradiaphragmatiques

D'après Schmidt et al., ICM, 2013 (131)

EMG, électromyogramme ; RMS, Root Mean Square ; AUC, Area Under Curve

2.2 Pression d'occlusion des voies respiratoires (P0.1)

L'évaluation de l'intensité de la commande centrale est souvent limitée à la recherche, avec peu de techniques disponibles au chevet du patient. Une mesure simple et non invasive est la P0.1 ou pression aux voies respiratoires occluses mesurée 100 ms après le début de l'inspiration (135). La P0.1 est une mesure fiable de la commande centrale du fait de l'absence de réaction consciente ou inconsciente à la charge mécanique avant les 150 ms suivant une occlusion inattendue. Il existe une bonne corrélation entre la P0.1 et l'effort inspiratoire mesuré soit par le travail respiratoire soit par le produit pression-temps (136, 137). Il est important de noter que la P0.1 reste fiable en cas de faiblesse des muscles respiratoires (138). La P0.1 est aujourd'hui automatiquement mesurée par les ventilateurs modernes de réanimation.

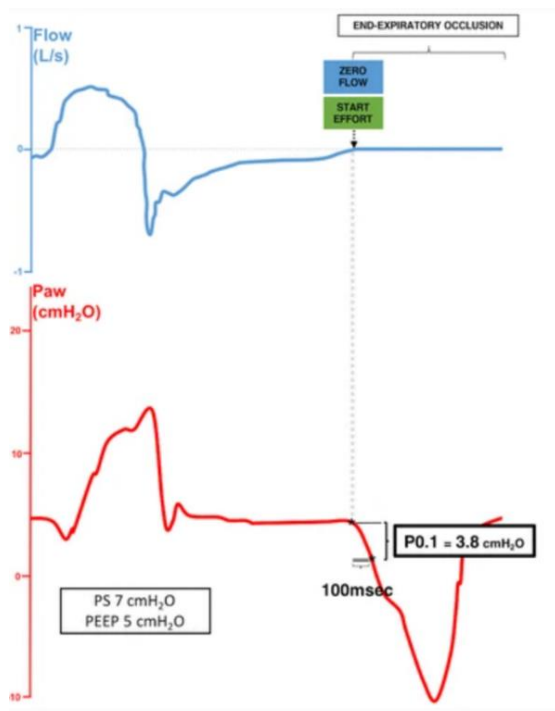


Figure 10 : P0.1 : pression d'occlusion des voies respiratoires
D'après Telias et al., ICM, 2018 (139)

3. Quantification des asynchronies patient-ventilateur

L'asynchronie patient-ventilateur se définit comme 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 (140, 141). Longtemps sous-estimée, la prévalence des asynchronies patient-ventilateur est aujourd'hui mieux connue. Dans une étude de prévalence conduite chez 43 patients hospitalisés en réanimation et ventilés sur sonde d'intubation (81), l'indice d'asynchronie (IA), défini comme la proportion de cycles asynchrones, était estimé à 2,1%. La proportion de patients présentant une asynchronie sévère, définie par un IA > 10 %, était de 24 %. Une étude plus récente (142) conduite chez 50 patients a mis en évidence des résultats comparables avec un IA médian de 3,4 % et une asynchronie sévère (IA > 10 %) chez 25 % des patients. En réanimation, la prévalence des asynchronies patient-ventilateur semble donc être élevée.

Un certain nombre de travaux suggèrent qu'une prévalence élevée d'asynchronies patient-ventilateur est associée à une altération du pronostic des patients de réanimation. Ainsi, les patients intubés présentant une asynchronie patient-ventilateur marquée ont une durée de ventilation mécanique plus élevée et nécessitent plus fréquemment la réalisation d'une trachéotomie (81, 142).

4. Variabilité respiratoire cycle-à-cycle

Au repos, la ventilation spontanée n'est pas monotone. Il est ainsi rare d'observer deux cycles respiratoires successifs en tous points superposables et identiques (143).

Cette variabilité « cycle à cycle », éminemment physiologique (143), peut être très simplement appréhendée par le calcul du coefficient de variation qui se définit comme l'écart-type rapporté à la moyenne (144). Les valeurs « normales » du coefficient de variation des principaux descripteurs du profil ventilatoire ne sont pas formellement établies. À titre d'exemple, les coefficients de variation du volume courant, de la fréquence respiratoire et du temps inspiratoire rapporté à la durée totale du cycle étaient respectivement de $33,0 \pm 14,9 \%$, $20,8 \pm 11,5 \%$, et $17,7 \pm 6,5 \%$ chez 65 volontaires sains après 15 minutes de ventilation spontanée (143, 145). Cette variabilité est donc physiologique et témoigne du niveau de contrainte imposé à l'appareil respiratoire : plus le niveau de contrainte est faible, plus la variabilité est élevée, et réciproquement. En conditions pathologiques, la diminution de cette variabilité cycle à cycle est liée à l'existence de contraintes mécaniques s'exerçant sur l'appareil respiratoire. Dans ce sens, l'application de charges chimiques ou mécaniques à l'appareil respiratoire de volontaires sains diminue la variabilité du comportement ventilatoire (146, 147). De même, une diminution de la variabilité respiratoire est observée chez les patients atteints de pathologies respiratoires (148).

Chez le sujet sain éveillé, la variabilité respiratoire tend à diminuer en réponse à la charge mécanique (146). Au cours du sevrage de la ventilation mécanique, une relation inverse entre la variabilité cycle-à-cycle du volume courant divisé par le temps inspiratoire et la compliance dynamique du système respiratoire a été rapportée (149). En revanche, la décharge du système respiratoire avec des niveaux d'assistance croissants augmente la variabilité respiratoire cycle-à-cycle (150). La relation charge-capacité du système respiratoire est donc un déterminant majeur de la variabilité respiratoire : plus la charge est élevée, plus la variabilité est faible.

Chapitre 1 Dyspnée et activité électromyographique des muscles inspiratoires pendant le sevrage de la ventilation mécanique

Bien que la dyspnée soit un symptôme clé de l'insuffisance respiratoire aiguë, elle ne figure pas parmi les critères d'échec de l'épreuve de ventilation spontanée qui est réalisée chez les patients intubés afin d'aider à déterminer s'ils peuvent être sevrés de la ventilation artificielle. La dyspnée n'est en général pas recueillie durant cette épreuve. Pourtant, la dyspnée est un symptôme facile à recueillir, quantifier et pourrait être utilisé pour suivre l'épreuve de ventilation spontanée.

La dyspnée survient lorsque la commande centrale augmente en réponse à un déséquilibre charge capacité du système nerveux central. Il convient de noter que le mécanisme par lequel l'augmentation de la commande centrale accroît la dyspnée n'a pas été entièrement établi. En particulier, il n'est pas démontré si la dyspnée est plus étroitement liée à la commande respiratoire centrale destinée au diaphragme ou aux muscles inspiratoires extradiaphragmatiques.

Notre premier objectif était de déterminer si l'évolution de la dyspnée est un critère fiable d'échec de l'épreuve et de comparer la dyspnée aux autres critères d'échec du sevrage afin de déterminer si le recueil de la dyspnée doit faire partie du suivi de toutes les épreuves de ventilation spontanée. Notre deuxième objectif était d'établir la relation entre la dyspnée et les activités EMG respective du diaphragme et de deux muscles inspiratoires extradiaphragmatiques, à savoir le muscle intercostal parasternal et le muscle *Alae Nasi*.

Nous avons quantifié la dyspnée au cours d'une épreuve de ventilation spontanée. Nous avons simultanément recueilli l'activité EMG du diaphragme ainsi que celle de deux autres muscles inspiratoires, le muscle intercostal parasternal et le muscle *Alae Nasi*.

Trente et un patients ont été inclus. Les résultats peuvent être résumés comme suit. Pendant l'épreuve de ventilation spontanée, 1) la dyspnée est un critère fiable de succès ou

échec du sevrage, ce qui suggère que l'EVA dyspnée pourrait devenir un outil de décision clinique utile pour surveiller l'épreuve de ventilation spontanée, 2) la dyspnée semble être plus étroitement liée à l'activité EMG des muscles inspiratoires extradiaphragmatiques qu'à l'activité EMG du diaphragme.

Ce travail a fait l'objet d'une publication dans le journal *Annals of Intensive Care*.

Chapitre 2 La ventilation assistée proportionnelle soulage la dyspnée cliniquement significative chez les patients ventilés en réanimation

Avec la VSAI, le mode d'assistance ventilatoire partielle le plus largement utilisé, un niveau de pression constant et prédéfini assiste chaque inspiration, quel que soit l'effort inspiratoire du patient. Une inadéquation entre l'effort inspiratoire du patient et le niveau d'assistance est donc susceptible de se produire. La PAV est un mode de ventilation mécanique qui ajuste en temps réel le niveau d'assistance à l'intensité de l'effort inspiratoire du patient, ce qui permet d'éviter la sous- et la sur-assistance (81, 89, 90, 95, 151, 152). Peu de données sont actuellement disponibles concernant l'impact de la PAV sur la dyspnée (81, 87, 89-92, 151, 152).

Notre première hypothèse était que la PAV soulagerait la dyspnée de façon plus efficace que la VSAI. Nous avons également émis l'hypothèse que cet effet bénéfique de la PAV sur la dyspnée serait associé 1) à une diminution de la commande centrale et 2) à une augmentation de la variabilité du profil respiratoire, témoins d'une amélioration de l'équilibre charge-capacité (27, 29, 72, 90-93, 153), 3) à une diminution de la prévalence des asynchronies patient-ventilateur.

Chez 34 patients intubés présentant une dyspnée significative, nous avons mesuré la dyspnée, l'EMG des muscles intercostaux parasternaux et les muscles *Alae Nasi*, ainsi que la pression et le débit aux voies aériennes. Nous avons quantifié la prévalence des principales asynchronies patient-ventilateur ainsi que le coefficient de variation (écart type rapporté à la moyenne, quantifiant la variabilité cycle-à-cycle) de plusieurs descripteurs du profil respiratoire. Les patients ont été étudiés dans trois conditions bien distinctes : 1) en VSAI à l'état de base, 2) en VS-AI après personnalisation des réglages, 3) en PAV.

Nos résultats peuvent être résumés comme suit. Chez les patients présentant une dyspnée cliniquement significative en VSAI, 1) la PAV et les réglages personnalisés de la VSAI

soulagent la dyspnée, 2) la PAV et les réglages personnalisés de la VSAI diminuent l'activité EMG des muscles inspiratoires, suggérant une diminution de l'activité de la commande centrale, 3) la variabilité respiratoire est plus élevée en PAV que dans les autres conditions et est inversement corrélée à la dyspnée, suggérant un meilleur équilibre charge - capacité, 4) la PAV est plus efficace que les réglages personnalisés de la VSAI pour réduire les asynchronies patient-ventilateur.

À notre connaissance, il s'agit de la première étude ayant comparé des réglages personnalisés de la VSAI à la PAV chez des patients sous ventilation mécanique présentant une dyspnée cliniquement significative. Dans cette étude, nous confirmons que de simples modifications des réglages du ventilateur peuvent suffire à réduire la dyspnée de façon significative.

Nos résultats suggèrent par ailleurs que le soulagement de la dyspnée résulte d'une réduction de la charge respiratoire, qui à son tour a réduit l'intensité de la commande centrale, comme l'illustre la diminution de l'amplitude des activités EMG des muscles inspiratoires.

Toutefois, la diminution de la dyspnée était associée à une augmentation concomitante du volume courant, ce qui montre que soulager la dyspnée peut aller à l'encontre des recommandations sur la ventilation protectrice, lesquelles suggèrent l'utilisation de volumes courants réduits (72).

Ce travail a fait l'objet d'une publication dans le journal *Annals of Intensive Care*.

Chapitre 3 Interventions sensorielles afin de soulager la dyspnée chez les patients sous ventilation mécanique en réanimation

En cas de déséquilibre charge-capacité des muscles respiratoires, ce qui est fréquent chez les patients de réanimation, l'augmentation de l'assistance ventilatoire est particulièrement efficace pour réduire l'intensité de la commande centrale de la respiration et soulager la dyspnée. Cependant, les recommandations d'utilisation d'une ventilation protectrice peuvent limiter cette option (76, 154) et conduire à un dilemme clinique difficile. Sur le plan thérapeutique, cela implique un potentiel changement de paradigme : passer de traitements ciblant l'appareil respiratoire (composante sensorielle) à des traitements ciblant le cerveau (155) et pouvant même le « tromper » (composantes émotionnelles et affectives). En dehors de la réanimation, lorsqu'il n'est pas possible de corriger l'état physiologique responsable de la dyspnée, des approches alternatives ont été décrites (156). Diriger un flux d'air vers le visage soulage la dyspnée (21, 64), probablement parce que le cerveau interprète la stimulation trigéminal correspondante comme une augmentation du trafic afférent lié à la respiration, permettant le concept de « tromper le cerveau » (157). La musique peut également soulager la dyspnée (31), possiblement en raison d'une distraction de l'attention ou d'un effet de réduction de l'anxiété : concept d' « apaisement de l'esprit » (158).

Nous avons émis l'hypothèse que des interventions ciblées sur le cerveau (stimulation du trijumeau et stimulation auditive) réduiraient l'intensité de la dyspnée chez les patients sous ventilation mécanique en réanimation et que cela se produirait indépendamment de réductions concomitantes de la commande centrale respiratoire. Nous avons également souhaité étudier l'impact respectif de ces interventions sur les dimensions sensorielles, affectives et émotionnelles de la dyspnée.

Chez 46 patients sous ventilation mécanique depuis plus de 48 heures et signalant une dyspnée, nous avons d'abord augmenté l'assistance ventilatoire, puis administré, dans un ordre

aléatoire, une stimulation auditive (musique relaxante vs. « bruit rose ») et une stimulation par un flux d'air (visage vs. membres inférieurs). La dyspnée a été évaluée à l'aide d'une EVA et du Multidimensionnal Dyspnea Profil. La commande respiratoire centrale a été évaluée grâce à l'activité électromyographique des muscles *Alae Nasi* et parasternaux et la P0.1.

Les principaux résultats de cette étude sont que les deux interventions sensorielles ciblées sur le cerveau (stimulation du nerf trijumeau par un flux d'air dirigé vers le visage et l'écoute d'une pièce musicale relaxante) ont soulagé la dyspnée chez des patients sous ventilation mécanique en réanimation. Ce soulagement concernait à la fois les dimensions sensorielles, émotionnelles et affectives de la dyspnée. En outre, ce soulagement s'est produit indépendamment de l'intensité de la commande centrale de la respiration. En revanche, l'augmentation de l'assistance ventilatoire, une intervention axée sur l'appareil respiratoire, n'a été efficace que dans la dimension sensorielle et s'est faite de manière concomitante avec une diminution de l'intensité de la commande centrale. Ces données indiquent que la commande respiratoire centrale n'est pas à elle seule suffisante pour expliquer la dyspnée, étant donné 1) qu'il est possible de diminuer la dyspnée sans modifier notablement l'intensité de la commande centrale, 2) que la modulation des composantes émotionnelles et affectives de la dyspnée supprime la corrélation entre la dyspnée et l'intensité de la commande centrale.

Dans notre étude, l'augmentation de l'assistance ventilatoire a atténué la composante sensorielle de la dyspnée, ce qui correspond très probablement à un meilleur équilibre charge-capacité de l'appareil respiratoire et à une réduction de la commande centrale, comme en témoigne la diminution de la P0.1 et de l'activité des EMG des muscles inspiratoires. Il est à noter que cette augmentation d'assistance n'a pas interféré avec les composantes émotionnelles et affectives de la dyspnée et que, comme attendu, l'efficacité de cette thérapeutique a été associée à une augmentation du volume courant, ce qui pourrait être délétère chez les patients à la phase aiguë d'une pathologie respiratoire. Les deux stimulations sensorielles (flux d'air sur

le visage et musique relaxante) ont également diminué la dimension sensorielle de la dyspnée mais cet effet a été obtenu sans modification du volume courant et indépendamment de toute modification de la commande respiratoire centrale. Cela a été bien illustré par l'observation d'une perte de la corrélation entre la dyspnée et la commande respiratoire centrale. Le soulagement de la dyspnée sans modification de l'équilibre charge-capacité suggère que le mécanisme de décharge corollaire n'est pas le seul impliqué dans la pathogenèse de la dyspnée. Ainsi, il est important de souligner que, contrairement à l'augmentation de l'assistance ventilatoire, les deux stimulations sensorielles ont été efficaces pour réduire les composantes émotionnelles et affectives de la dyspnée.

Ce travail a été soumis pour publication dans *l'European Respiratory Journal* et est en cours d'évaluation.

Chapitre 4 L'augmentation du débit de gaz de balayage à travers la membrane réduit la dyspnée et la commande centrale respiratoire chez les patients traités par ECMO veino-artérielle

La dyspnée survient lorsque la commande centrale augmente à la suite d'un déséquilibre charge-capacité du système respiratoire. La PaCO₂ constitue un puissant stimulus de la commande centrale respiratoire. L'augmentation de la PaCO₂ peut provoquer une dyspnée, et ce, même indépendamment de la contraction des muscles respiratoires (159, 160).

L'ECMOva offre la possibilité de moduler l'extraction de CO₂ en faisant varier le débit de gaz de balayage à travers la membrane d'ECMO. Chez les patients sous ECMO veino-veineuse, il est notamment montré que l'augmentation du débit de balayage à travers la membrane d'ECMO diminue l'intensité de la commande respiratoire centrale. Toutefois, il n'existe à notre connaissance pas de donnée concernant l'impact du débit de gaz de balayage à travers la membrane d'ECMO sur la dyspnée (161-163).

Notre hypothèse était que, chez des patients non intubés et assistés par ECMOva pour une défaillance cardiaque aiguë, présentant une dyspnée significative, la modulation du débit de balayage à travers la membrane d'ECMOva soulagerait la dyspnée.

Chez 21 patients sous ECMOva pour un choc cardiogénique et présentant une dyspnée, le débit de balayage a été augmenté jusqu'à +6 L/min en trois étapes successives de +2 L/min chacune. La dyspnée a été évaluée au moyen d'une EVA et du profil multidimensionnel de la dyspnée. La commande centrale a été évaluée par l'activité électromyographique des muscles *Alae Nasi* et parasternaux.

Les principaux résultats montrent que, chez des patients sous ECMOva présentant une dyspnée, l'augmentation du débit de balayage soulage la dyspnée avec une réduction parallèle de l'intensité de la commande centrale respiratoire. Bien que l'augmentation du débit de balayage diminue toutes les composantes de la dyspnée, elle est plus marquée pour la composante sensorielle de la dyspnée que pour les composantes émotionnelles et affectives. De

plus, il y a une corrélation significative entre la commande centrale respiratoire et la composante sensorielle de la dyspnée, alors qu'il n'y a aucune corrélation entre la commande centrale respiratoire et les composantes émotionnelles et affectives de la dyspnée.

Le fait que l'augmentation du débit de balayage à travers la membrane est associée à une forte diminution de la composante sensorielle de la dyspnée par rapport aux composantes émotionnelles et affectives, suggère que les changements d'intensité de la dyspnée en réponse à la modulation de l'élimination du CO₂ sont plus étroitement liés à la composante sensorielle de la dyspnée qu'aux composantes affectives et émotionnelles. Le CO₂ étant un stimulus majeur de la commande centrale, nos résultats suggèrent que celui-ci est l'un des principaux déterminants de la composante sensorielle de la dyspnée, mais pas de ses composantes émotionnelles et affectives. Ceci est renforcé par le fait que, dans notre étude, la commande centrale évaluée par l'activité EMG des muscles *Alae Nasi* et intercostaux parasternaux est significativement corrélée avec la composante sensorielle de la dyspnée, mais pas avec les composantes émotionnelles et affectives de la dyspnée.

Ce travail est finalisé et sera soumis prochainement au journal *Anesthesiology*.

Conclusion et perspectives

La présente thèse s'est intéressée à évaluer des interventions thérapeutiques visant à soulager la dyspnée chez les patients de réanimation. Plus spécifiquement, cette thèse a exploré des cibles potentielles permettant « d'atténuer » la composante sensorielle de la dyspnée et de « moduler » les composantes affectives et émotionnelles, afin de mieux caractériser la part de chacune dans le soulagement de la dyspnée. Cette thèse s'est enfin intéressée au lien entre, d'une part, les différentes composantes de la dyspnée, et d'autre part, la commande respiratoire centrale. Les principales conclusions et les perspectives de ce travail sont discutées ci-dessous.

Nous avons établi dans un premier temps (**Chapitre 1**) que la dyspnée semble être plus étroitement liée à l'activité EMG des muscles inspiratoires extradiaphragmatiques qu'à l'activité EMG du diaphragme. Parallèlement, nous avons montré (**Chapitres 2 et 3**) qu'en l'absence des propriétés physiologiques de l'appareil respiratoire, l'amélioration de l'équilibre charge-capacité par la personnalisation de la VSAI ou par utilisation de la PAV diminue la dyspnée, parallèlement à la commande respiratoire centrale. Il est possible d'envisager que la diminution de la commande centrale résultant d'une amélioration de l'équilibre charge – capacité diminue la dyspnée, mais il ne peut être exclu que le soulagement de la dyspnée par une augmentation du trafic afférent ne réduise lui aussi la commande centrale. En outre, nous avons montré (**Chapitre 3**) qu'en l'absence des propriétés physiologiques de l'appareil respiratoire, la stimulation du nerf trijumeau par un flux d'air dirigé vers le visage et l'écoute d'une pièce musicale relaxante permettent de diminuer toutes les composantes de la dyspnée, sans diminution notable de l'intensité de la commande respiratoire centrale, et ce, principalement grâce à une modulation des composantes affectives et émotionnelles de la dyspnée. Ces éléments vont contre l'idée que la dyspnée est un déterminant de la commande respiratoire centrale, puisqu'il est possible de diminuer la dyspnée sans modifier cette commande. De plus, ces données indiquent que la commande respiratoire centrale n'est pas à elle seule suffisante

pour expliquer la dyspnée puisqu'il est possible de la diminuer sans modifier notablement l'intensité de la commande centrale, mais aussi parce que la modulation des composantes émotionnelles et affectives de la dyspnée supprime la corrélation entre la dyspnée et l'intensité de la commande centrale. Enfin, nous avons montré (Chapitre 4) qu'en l'absence de modification de l'état physiologique respiratoire, ni de modification des afférences respiratoires avec une adaptation de la ventilation (Chapitre 3 et Chapitre 4), ni de modification des pseudo-afférences respiratoires avec une stimulation du trijumeau (Chapitre 3 : flux d'air), augmenter l'épuration du CO₂ en augmentant le débit de balayage de gaz dans la membrane d'ECMO diminue la dyspnée ainsi que l'intensité de la commande centrale respiratoire. L'existence d'une corrélation significative entre la commande respiratoire centrale et la composante sensorielle de la dyspnée, sans corrélation entre la commande centrale et les composantes émotionnelles et affectives de la dyspnée renforce l'idée qu'il existe un lien de causalité entre commande respiratoire centrale et composante sensorielle de la dyspnée.

Si nos travaux apportent des informations nouvelles sur l'implication respective des composantes sensorielles et affectives dans le soulagement de la dyspnée chez le patient de réanimation, ils suscitent aussi de nombreuses interrogations qui justifient de poursuivre nos recherches.

En effet, si l'impact à court terme des thérapeutiques employées dans nos travaux sur la dyspnée a pu être précisément étudié, l'impact à long terme n'est lui pas connu. Il conviendra donc de mener des études sur cet impact à long terme afin d'évaluer les parts respectives des composantes sensorielles, émotionnelles et affectives sur cette période et le caractère persistant de leurs effets. Ainsi, notre travail, notamment le Chapitre 3, fournit la justification scientifique à des essais cliniques à venir évaluant la solidité à long terme des interventions ciblées sur le cerveau utilisée (musique relaxante, flux d'air sur le visage) afin de soulager de la dyspnée. Ces

travaux à long terme permettront d'évaluer d'éventuels effets indésirables de ces thérapeutiques par stimulation sensorielle.

Si notre travail a permis de montrer qu'il est possible d'agir sur les différentes composantes, le caractère cumulatif de leurs effets n'est pas connu. Une évaluation de la dyspnée à partir d'une approche associant des thérapeutiques ciblant simultanément les différentes composantes sensorielles, émotionnelles et affectives permettrait de répondre à cette question.

Cette thèse a permis de progresser sur la connaissance des mécanismes des différentes composantes de la dyspnée. Cependant, en pratique, chaque situation clinique est différente et les thérapeutiques actuellement disponibles et efficaces pour soulager la dyspnée sont peu nombreuses. De la même façon que les mécanismes de la dyspnée sont multiples, son traitement idéal est probablement multimodal et se doit d'être adapté à chaque contexte. Un plus grand choix et une plus grande facilité d'options thérapeutiques pour soulager la dyspnée permettront de favoriser le dépistage et le diagnostic de cet inconfort chez une large partie des patients de réanimation. Il convient donc d'explorer une approche multimodale du soulagement de la dyspnée en réanimation.

Chez les patients atteints de BPCO, l'hypnose soulage la dyspnée (164). Des études sont en cours chez le sujet sain soumis à une dyspnée expérimentale (NCT02792738) ou chez des patients atteints de BPCO afin d'évaluer plus spécifiquement l'impact de l'hypnose sur la composante émotionnelle de la dyspnée (NCT04010825). L'hypnose pourrait ainsi être utilisée pour soulager la dyspnée en réanimation et il serait utile d'étudier de façon concomitante l'activité de la commande respiratoire centrale au cours de la séance d'hypnose.

Il a été montré que l'observation de la dyspnée par un tiers provoque une dyspnée légère à modérée, un affect négatif et une modification électroencéphalographique en l'absence de modification de l'état physiologique respiratoire (165). Cette dyspnée est appelée « dyspnée vicariante ». Il pourrait en être de même pour le soulagement d'une dyspnée ; ainsi la visualisation

d'une scène avec un acteur mimant une situation dyspnéisante puis son soulagement serait susceptible d'obtenir chez le patient dyspnéique une sensation de soulagement.

Le syndrome de détresse respiratoire aiguë, nécessite chez certains patients une ventilation artificielle « ultra-protectrice », qui consiste à limiter le volume courant insufflé à 4 ml/kg. Les poumons sont alors mis au repos pendant qu'une ECMO veino-veineuse permet d'assurer l'hématose. Certains de ces patients peuvent être maintenus éveillés le temps de leur prise en charge. Cependant la sévérité de l'atteinte respiratoire et, probablement, l'absence de stimulation des récepteurs à l'étirement en raison du faible volume courant délivré pourraient être responsables d'une dyspnée persistante. Évaluer si la dyspnée ressentie par ces patients présentant un syndrome de détresse respiratoire aiguë est liée à l'absence de stimulation des récepteurs à l'étirement en raison du faible volume courant délivré aux patients serait intéressant et la remise en charge du poumon par augmentation progressive du volume courant devrait ainsi permettre de soulager secondairement la dyspnée.

Plusieurs questions physiologiques sont également nées de ce travail et pourront être explorées dans le futur. Ainsi, il sera important d'explorer plus précisément comment la modulation du CO₂ affecte la modulation du schéma respiratoire chez les patients sous ECMOva, notamment en ayant recours à des outils diagnostiques permettant d'analyser la ventilation dans ces conditions, tel que la tomographie par impédance électrique.

Une analyse secondaire des résultats obtenus dans le **Chapitre 3** en analysant la variabilité respiratoire des signaux enregistrée pourrait permettre de déterminer l'impact respectif des différents stimulus (incrémentations de l'aide inspiratoire, flux d'air sur le visage et musique relaxante) sur la variabilité respiratoire, et donc l'équilibre charge-capacité. Si on peut faire l'hypothèse que l'incrémentations d'aide inspiratoire, qui améliore l'équilibre charge-capacité, s'accompagnera d'une augmentation de la variabilité cycle-à-cycle, il sera important d'explorer comment évoluera cette variabilité lors des stimulations sensorielles et auditives « trompant » le cerveau.

Enfin, les travaux réalisés autour de la dyspnée et de son soulagement ont permis d'envisager de transposer le raisonnement à d'autres symptômes multidimensionnels pouvant partager des mécanismes physiopathologiques ou des zones d'activation cérébrales. Ainsi, la soif est mal reconnue dans la pratique des unités de soins intensifs. Or, les études ont montré qu'il s'agit de l'un des symptômes les plus répandus, les plus intenses et les moins bien traités dans cette population (166, 167) et que ce symptôme est associé à un inconfort physique (168). Cependant, la soif passe souvent inaperçue et n'est pas traitée (169). Nous pourrions ainsi mener une étude prospective observationnelle chez des patients sous ventilation mécanique capables de communiquer afin de mieux comprendre la prévalence, l'intensité, les mécanismes et la valeur pronostique de la soif. Dans un second temps, il serait intéressant d'étudier dans notre population des patients ayant reçu des stimulations sensorielles puis dans une étude spécifiquement dédiée si ces stimulations sont capables d'entraîner une diminution de la sensation de soif en trompant le cerveau.

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Travaux scientifiques contributifs de la thèse

RESEARCH

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Dyspnea and the electromyographic activity of inspiratory muscles during weaning from mechanical ventilation

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Abstract

Rationale: Dyspnea, a key symptom of acute respiratory failure, is not among the criteria for spontaneous breathing trial (SBT) failure. Here, we sought (1) to determine whether dyspnea is a reliable failure criterion for SBT failure; (2) to quantify the relationship between dyspnea and the respective electromyographic activity of the diaphragm (EMGdi), the parasternal (EMGpa) and the *Alae nasi* (EMGan).

Methods: Mechanically ventilated patients undergoing an SBT were included. Dyspnea intensity was measured by the Dyspnea-Visual Analogic Scale (Dyspnea-VAS) at the initiation and end of the SBT. During the 30-min SBT or until SBT failure, the EMGdi was continuously measured with a multi-electrode nasogastric catheter and the EMGan and EMGpa with surface electrodes.

Results: Thirty-one patients were included, SAPS 2 (median [interquartile range]) 53 (37–74), mechanically ventilated for 6 (3–10) days. Seventeen patients (45%) failed the SBT. The increase in Dyspnea-VAS along the SBT was higher in patients who failed (6 [4–8] cm) than in those who passed (0 [0–1] cm, $p=0.01$). The area under the receiver operating characteristics curve for Dyspnea-VAS was 0.909 (0.786–1.032). The increase in Dyspnea-VAS was significantly correlated to the increase in EMGan (Rho = 0.42 [0.04–0.70], $p < 0.05$), but not to the increase in EMGpa (Rho = -0.121 [-0.495 to -0.290], $p=0.555$) and EMGdi (Rho = -0.26 [-0.68 to 0.28], $p=0.289$).

Conclusion: Dyspnea is a reliable criterion of SBT failure, suggesting that Dyspnea-VAS could be used as a monitoring tool of the SBT. In addition, dyspnea seems to be more closely related to the electromyographic activity of the *Alae nasi* than of the diaphragm.

Keywords: Mechanical ventilation, Dyspnea, Clinical study, Physiology

Introduction

In the intensive care unit (ICU), weaning from mechanical ventilation follows a well-described two-step assessment. First, readiness-to-wean criteria should be searched for, at least on a daily basis [1]. Second, once

these criteria are present, a spontaneous breathing trial (SBT) is performed to evaluate whether the patient can breathe without assistance from the ventilator [1]. The SBT is deemed a failure if the patient develops clinical signs considered as reflecting respiratory distress, which are considered to relate to an imbalance between respiratory system loading and respiratory muscle capacity [1–4]. These signs of acute respiratory failure and subsequent SBT failure are deemed objective (polypnea $> 35/\text{min}$, $\text{PaO}_2 \leq 50\text{--}60$ mmHg with $\text{FiO}_2 \geq 50\%$ or $\text{SpO}_2 < 90\%$, increase between the initiation and end of

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the SBT in $\text{PaCO}_2 > 8$ mmHg, tachycardia $> 140/\text{min}$) and subjective (signs considered as reflecting respiratory distress, increased accessory muscle activity, agitation and anxiety) [1]. If the SBT is successful, criteria for extubation are searched for. The current procedure applied within a classic population of intensive care patients is associated with 70% or more weaning success in randomized or observational studies [5, 6].

Although dyspnea is a key symptom of acute respiratory failure, dyspnea is not listed among the criteria for SBT failure and is often not even collected and therefore ignored during the SBT. Yet, dyspnea is a self-reported symptom that is easy to collect and to quantify in communicative patients, and could be used as a criterion of SBT failure [7, 8]. Dyspnea occurs when the inadequacy between the outflowing neural drive and the corresponding instreaming afferent return increases [9], which occurs in the event of respiratory system load capacity imbalance. It is of note that the mechanism through which increased respiratory drive increases dyspnea has not been fully established. In particular, it is not clear whether dyspnea is more closely linked to the central output to the diaphragm or to extradiaphragmatic inspiratory muscles [8, 9].

Here, we assessed dyspnea during an SBT. Our first objective was to determine whether dyspnea change is a reliable criterion of weaning failure and to compare dyspnea to other criteria for weaning failure to determine whether dyspnea collection should be part of the follow-up of all SBTs in an effort to improve the current MV weaning procedure. Our second objective was to establish the relationship between dyspnea and the respective electromyographic activity (EMG) of the diaphragm and two extradiaphragmatic inspiratory muscles, namely the parasternal intercostal and the *Alae nasi*.

Patients and methods

This observational, single-center prospective study was conducted over a 1-year period in the 10-bed medical intensive care unit (ICU) of the respiratory and ICU Division of La Pitié-Salpêtrière Hospital, Paris, France.

Patients

The study was approved by the Comité de Protection des Personnes Ile de France VI (No. 84-14). Informed consent was obtained from patients.

Patients were eligible as soon as they met the following criteria: (1) intubation and mechanical ventilation for more than 24 h, and (2) the predefined readiness-to-wean criteria, adapted from the 2007 international consensus conference [1], on daily screening and the physician in charge decided to initiate an SBT [1]. Predefined readiness-to-wean criteria were the following:

resolution of the acute phase of the disease for which the patient had received invasive mechanical ventilation, low bronchial congestion, adequate cough, adequate oxygenation defined by $\text{SpO}_2 > 90\%$ with $\text{FiO}_2 \leq 40\%$ and positive end-expiratory pressure (PEEP) ≤ 8 cm H_2O , respiratory rate ≤ 40 breathes/min, a Ramsay sedation scale < 4 and stable cardiovascular status (heart rate ≤ 120 beats/min, systolic arterial blood pressure ≤ 180 mmHg and no or minimal vasopressors (norepinephrine < 5 $\mu\text{g}/\text{kg}/\text{min}$). Patients < 18 years, with neuromuscular diseases, those for whom life support would be withheld or withdrawn and patients for whom the repeated assessment of dyspnea was likely to be difficult (auditory or visual impairment, insufficient command of French, known prior cognitive or psychiatric disorder, ICU delirium) were not included in the study.

Study protocol

All patients were ventilated using a Servo-i ventilator (Maquet Critical Care, Solna, Sweden) equipped with the standard commercial version of the NAVA module.

The standard nasogastric feeding tube was removed and replaced by an electromyography activity of the diaphragm catheter consisting of a 16-French gastric tube equipped with electrodes.

As soon as the patients met the readiness-to-wean criteria, a 30-min SBT was performed with the patient connected to the ventilator with a pressure support level of 7 cm H_2O and zero end-expiratory pressure. The FiO_2 was adjusted during the SBT so as to obtain an SpO_2 of between 90 and 95%. Electromyographic recording was performed during the whole time of the SBT. The endotracheal tube was suctioned before starting recording.

Based on the criteria adapted from the 2007 international consensus conference [1], the SBT was considered a failure if at least one the following criteria was present: (1) $\text{SaO}_2 < 90\%$ with $\text{FiO}_2 \geq 50\%$; (2) acute respiratory distress ($\text{RR} \geq 40/\text{min}$, agitation, cyanosis); (3) systolic arterial blood pressure ≥ 180 mmHg; (4) sudden cardiac arrhythmias, and (5) respiratory acidosis ($\text{pH} < 7.32$ with $\text{PaCO}_2 \geq 50$ mmHg). If none of the above failure criteria was present, the SBT was considered successfully completed and extubation was considered. The patient was reconnected if signs of intolerance (see above) were present. The decision as to whether the SBT was passed or failed was based on the clinical judgment of the physician in charge of the patient, who was independent of the investigators.

Data acquisition

Anthropometric data and medical history were collected at inclusion.

Clinical variables Heart rate, systemic blood pressure and dyspnea were collected at the initiation and end of the SBT. Presence of neuromuscular weakness, defined by MRC score <48, was collected. Richmond Agitation Sedation Scale and Pain-Visual Analogue Scale (from 1 to 100 mm) were collected during the assessment that was the closest of the SBT. Medications received by the patient before and during the SBT were collected. Patients were considered able to consistently self-report dyspnea if the Dyspnea-Visual Analogue Scale (Dyspnea-VAS) variation did not exceed 1 cm for three consecutive measures [10, 11]. Dyspnea was quantified by placing a cursor on a 10 cm Dyspnea-Visual Analogue Scale (Dyspnea-VAS) bounded on the left by “no respiratory discomfort” and on the right by “worst imaginable respiratory discomfort”.

Airway pressure and flow Airway flow was measured with a pneumotachograph (Hans Rudolph, Kansas City, USA) inserted between the Y-piece and the endotracheal tube before being connected to a differential pressure transducer (Validyne, Northridge, USA). Airway pressure was measured at the Y-piece by a differential pressure transducer (Validyne, Northridge, USA).

Electromyography of extradiaphragmatic inspiratory muscles The EMG signal was collected by self-adhesive surface electrodes such as those commonly used to record the electrocardiogram signal in critically ill patients, with an interval of 2 cm between the two electrodes. Electrode positions varied according to the muscle being recorded. For the EMG of the parasternal intercostal muscles, electrodes were placed next to the second intercostal space as close as possible to the sternum. For the EMG of the *Alae nasi* muscles, electrodes were placed on the lateral surfaces of the nose (nostrils) [9]. EMG signals were amplified, sampled at a frequency of 10 kHz, and finally filtered between 40 and 500 Hz (PowerLab, ADInstruments, Dunedin, New Zealand). The signal was processed using the Labchart Peak Analysis module MLS380/8 (ADInstruments, Dunedin, New Zealand), which generates a root mean square of the EMG smoothed over 1-s fixed windows.

Electromyography of the diaphragm The EMG of the diaphragm was obtained from the multi-electrode nasogastric NAVA catheter, an esophageal probe that collects the EMG signal with bipolar electrodes in sequential order, after checking the correct positioning of the probe and the quality of the signal. An automated processing technique

tracks the displacement of the diaphragm [12]. A cross-correlation technique (for every second pair of electrodes) determines the position of the diaphragm along the array every 16 ms. Subtraction of opposite phase signals above and below the diaphragm results in a new signal: the “double-subtracted” signal. This double-subtracted signal is free from distance filtering. In addition, the signal-to-noise ratio is enhanced [12]. Diaphragm EMG was acquired at 100 Hz from the ventilator connected to a computer using commercially available software (Servo-i RCR, version 3.6.2, Maquet Critical Care), which generates a root mean square of the EMG. The root mean square of this signal is then calculated every 16 ms, and added to the RMS of the center signal [13, 14]. The resultant RMS values for every 16-ms sample can be graphically connected [15]. The RMS is linearly related to the number of motor units recruited and their firing rate. Finally, the electrocardiographic signal is detected and replaced by a value predicted from the previous diaphragm EMG value. To further reduce electrical noise disturbances and motion artifacts and to minimize electrocardiographic and electrical activity from the esophagus, the signal is eventually filtered with a cascade of filters.

Arterial blood gases Blood gases were sampled at the initiation and end of the SBT or earlier in case of intolerance using an arterial catheter.

Signal processing

Respiratory rate (RR) and tidal volume (V_T) were determined on a breath-by-breath basis and averaged for the first and last 5 min of the SBT recording (Labchart 7.3[®] software, ADInstruments, Dunedin, New Zealand).

Maximum EMG (EMG_{max}) and the area under the curve of the EMG during inspiratory time (EMG_{auc}) integrated from baseline to peak were calculated on a breath-by-breath basis. The first and last 5 min of the SBT were eventually averaged. Due to the variability of skin impedance [16, 17] and the patient’s morphology, EMG_{max} and EMG_{auc} values were normalized to EMG activity at initiation of the SBT.

Statistical analysis

Statistical analysis was performed with Prism 8.0 software (GraphPad Software, USA). Quantitative variables were described by their median and interquartile range. Changes in dyspnea, breathing pattern, hemodynamics and blood gas are expressed as the difference in variables between the initiation and end of the SBT. Change in EMG activity is expressed as the ratio of the EMG activity and the end of SBT to the EMG activity at the initiation of the SBT. Contribution of extradiaphragmatic recruitment to diaphragm activity is expressed as the ratio of the

EMG activity of the *Alae Nasi* to the EMG activity of the diaphragm. Categorical variables were expressed as absolute values and percentages. All analyses were performed with a type I error of 5%. Results were compared between the success and failure groups. Differences between groups were assessed with the Mann–Whitney test for continuous variables and the χ^2 tests for categorical variables. Correlations between variables were evaluated using the Spearman rank correlation coefficient. receiver operating characteristic (ROC) curves were performed to evaluate the performance of indices to detect SBT failure.

On the basis of previous studies that our team has conducted on this subject and data from the literature, which estimate the probability of failure to wean at 40% [18], we predict that a population of 30 patients would achieve a sufficient number of patients who fail SBT to analyze the variables that detect SBT failure. Because we anticipated missing data on the assessment of dyspnea and poor EMG quality in some patients, we increased the sample size to 50 patients.

Results

One hundred and forty-five patients with invasive mechanical ventilation for more than 24 h and eligible

for SBT were admitted during the study period. Two patients were less than 18 years old, three had auditory impairment, three had insufficient command of French, 26 refused to participate, and, a technical reason (equipment failure, weekend) could not allow inclusion in 61.

Fifty patients were included in the study, of whom five were excluded because dyspnea could not be assessed reliably and 14 because the EMG signal was of poor quality and could not be process or interpreted. Overall, 31 patients were enrolled, of whom 14 (45%) failed the SBT; among them, three were due to cardiac failure.

Patient characteristics are shown in Table 1. Age was 65 (61–71) years and SAPS II at ICU admission was 53 (37–74). Patients were mechanically ventilated for 6 (3–10) days. The reason for intubation was acute respiratory failure for 71%, coma for 13%, cardiac arrest for 6% and shock for 6%. All patients intubated due to coma passed their SBT. Other characteristics did not differ between patients who passed and those who failed the SBT. No patient was receiving sedation at the time of SBT. Prior to SBT, patients had received midazolam (74%), and propofol (90%). One patient (weaning success group) was received continuous morphine chlorhydrate intravenous infusion during SBT and a second one

Table 1 Characteristics of the study population

	All patients <i>n</i> = 31	SBT success <i>n</i> = 17	SBT failure <i>n</i> = 14	<i>p</i> value
Gender, male, <i>n</i> (%)	22 (71)	12 (70)	10 (71)	1.000
Age, year	65 (61–71)	65 (51–68)	71 (63–75)	0.019
Body mass index, kg.m ⁻²	25 (21–30)	26 (21–31)	24 (21–29)	0.726
Duration of mechanical ventilation prior to inclusion, days	6 (3–10)	7 (4–9)	4 (3–10)	0.509
Comorbidities				
Chronic respiratory disease, <i>n</i> (%)	7 (23%)	3 (18%)	4 (29%)	0.670
Chronic heart disease, <i>n</i> (%)	4 (13%)	1 (6%)	3 (21%)	0.304
Diabetes, <i>n</i> (%)	3 (10%)	2 (12%)	1 (7%)	1.000
Cirrhosis, <i>n</i> (%)	7 (23%)	5 (29%)	2 (14%)	0.411
Neuromuscular weakness, <i>n</i> (%)	4 (13%)	1 (6%)	3 (21%)	0.304
Reason for intubation				
Acute respiratory failure, <i>n</i> (%)	22 (71)	10 (59)	12 (86)	0.101
Coma, <i>n</i> (%)	4 (13)	4 (24)	0 (0)	0.050
Cardiac arrest, <i>n</i> (%)	2 (6)	1 (6)	1 (7)	1.000
Shock, <i>n</i> (%)	2 (6)	1 (6)	1 (7)	1.000
Severity scores				
SAPS II at ICU admission	53 (37–74)	61 (39–80)	45.5 (30–61)	0.414
SOFA at inclusion	11 (7–14)	12.5 (9.5–14)	8.5 (6–12)	1.000
Pain assessment and level of sedation				
Pain-Visual Analogic Scale, mm	0 (0–20)	0 (0–15)	0 (0–20)	0.250
RASS	0 (0–0)	0 (0–0)	0 (0–0)	0.999

Data are provided as median (interquartile range) and number (%)

SBT spontaneous breathing trial; ICU intensive care unit; SAPS Simplified Acute Physiology Score; SOFA Sepsis-related Organ Failure Assessment; RASS Richmond Agitation Sedation Scale

(weaning success group) was receiving discontinuous morphine intravenous administration. The other patients did not receive morphine during SBT. In the days preceding the SBT, 87% of patients had received sufentanyl.

Dyspnea and criteria for SBT failure

Dyspnea, breathing pattern, hemodynamics and blood gas at the initiation and end of the SBT are reported in Table 2. At SBT initiation, dyspnea-VAS was no different between patients who passed the SBT and those who failed ($p=0.188$). Systolic blood pressure ($p=0.233$), PaCO₂ ($p=0.406$), pH ($p=0.212$) and SaO₂ ($p=0.462$) were also no different between patients who passed the

SBT and those who failed. Conversely, RR ($p=0.001$), RR/V_T ($p=0.031$) and heart rate ($p=0.014$) were higher in patients who failed the SBT than in those who passed, while PaO₂ was lower ($p=0.039$). At the end of the SBT, dyspnea-VAS was higher in patients who failed the SBT than in those who passed ($p=0.003$). Respiratory rate ($p=0.001$), heart rate ($p=0.001$) and systolic blood pressure ($p=0.016$) at the end of the SBT were also higher in patients who failed the SBT than in those who passed, while SaO₂ ($p=0.005$) was lower.

The change in dyspnea, breathing pattern, hemodynamics and blood gas between the initiation and end of the SBT is shown in Table 3. The change in

Table 2 Dyspnea, breathing pattern, hemodynamics and blood gas at the initiation and end of the spontaneous breathing trial

	Initiation of SBT				End of SBT			
	All patients n = 31	SBT success n = 17	SBT failure n = 14	p value	All patients n = 31	SBT success n = 17	SBT failure n = 14	p value
Dyspnea-VAS, mm	2 (0–2)	0 (0–2)	2 (2–5)	0.188	4 (0–10)	0 (0–4)	10 (8–10)	0.003
RR, min ⁻¹	23 (20–28)	20 (17–23)	28 (24–31)	0.001	27 (20–35)	22 (16–25)	35 (32–40)	0.001
V _T , ml	380 (328–476)	453 (372–557)	336 (283–388)	0.004	437 (334–551)	450 (370–563)	345 (271–513)	0.109
RR/V _T , min ⁻¹ ·ml ⁻¹	48 (41–77)	45 (31–63)	77 (50–95)	0.031	54 (39–74)	52 (35–68)	75 (47–113)	0.625
Heart rate, min ⁻¹	93 (83–102)	88 (72–105)	96 (89–102)	0.014	95 (83–110)	87 (76–101)	99 (91–114)	0.001
Systolic blood pressure, mmHg	136 (127–146)	136 (130–151)	132 (123–146)	0.233	143 (135–171)	139 (130–152)	158 (138–200)	0.016
PaO ₂ , mmHg	89 (79–120)	113 (79–130)	86 (73–94)	0.039	64 (59–78)	65 (60–86)	62 (65–75)	0.218
PaCO ₂ , mmHg	37 (32–46)	36 (32–42)	44 (33–52)	0.406	40 (35–45)	37 (34–41)	44 (41–66)	0.106
pH	7.45 (7.39–7.47)	7.43 (7.38–7.48)	7.45 (7.42–7.48)	0.212	7.42 (7.38–7.49)	7.42 (7.41–7.50)	7.39 (7.29–7.45)	0.150
SaO ₂ , %	97 (95–100)	98 (95–100)	97 (94–98)	0.462	93 (92–95)	95 (93–99)	91 (88–93)	0.005

SBT spontaneous breathing trial; *Dyspnea-VAS* Dyspnea-Visual Analog Scale; *RR* respiratory rate; *V_T* tidal volume; *IBW* ideal body weight; *SaO₂* arterial saturation of oxygen

Data are provided as median (interquartile range) and number (%)

Table 3 Change in dyspnea, breathing pattern, hemodynamics and blood gas between the initiation and end of the spontaneous breathing trial (SBT)

	SBT success (n = 17)	SBT failure (n = 14)	p value
Dyspnea-VAS, mm	0 (0–1)	6 (4–8)	0.006
RR, min ⁻¹	1 (– 2 to 3)	8 (4–13)	0.001
V _T , ml	– 7 (– 74 to 80)	– 29 (– 89 to 50)	0.844
RR/V _T	0 (– 9 to 27)	11 (– 16 to 29)	1.000
Heart rate, min ⁻¹	1 (– 3 to 2)	7 (0–19)	0.017
Systolic blood pressure, mmHg	2 (– 3 to 9)	31 (5–62)	0.020
PaO ₂ , mmHg	– 21 (– 40 to – 1.25)	– 21 (– 32.5 to 2)	0.910
PaCO ₂ , mmHg	0 (– 2 to 4)	4 (2–12)	0.161
pH	0.02 (– 0.02 to 0.03)	– 0.07 (– 0.12 to 0.01)	0.171
SaO ₂ , %	– 1 (– 3 to 0)	– 4 (– 8 to – 3)	0.036

The evolution is described by the difference in variables between the initiation and end of the spontaneous breathing trial

Data are provided as median (interquartile range) and number (%)

Dyspnea-VAS Dyspnea-Visual Analog Scale; *RR* respiratory rate; *V_T* tidal volume; *IBW* ideal body weight; *SaO₂* arterial saturation of oxygen

dyspnea-VAS ($p=0.006$), RR ($p=0.001$), heart rate ($p=0.017$), systolic blood pressure ($p=0.020$) and SaO_2 ($p=0.036$) between the initiation and end of the SBT was higher in patients who failed the SBT than in those who passed. There was no difference between patients who failed the SBT and those who passed in terms of change in V_T ($p=0.844$), RR/V_T ($p=1$), PaO_2 ($p=0.537$), $PaCO_2$ ($p=0.738$) and pH ($p=0.785$).

Figure 1 displays the ROC curve as failure criteria for the change in dyspnea-VAS, RR/V_T , respiratory rate,

PaO_2 , $PaCO_2$, pH, SaO_2 , heart rate and systolic blood pressure.

Correlation between the dyspnea-VAS and the PaO_2 , $PaCO_2$, SaO_2 and respiratory rate at the initiation and the end of spontaneous breathing trial is reported in Additional file 1: Fig. S1. Correlation between the change of dyspnea-VAS and the change in PaO_2 , $PaCO_2$, SaO_2 and respiratory rate is reported in Additional file 1: Fig. S2.

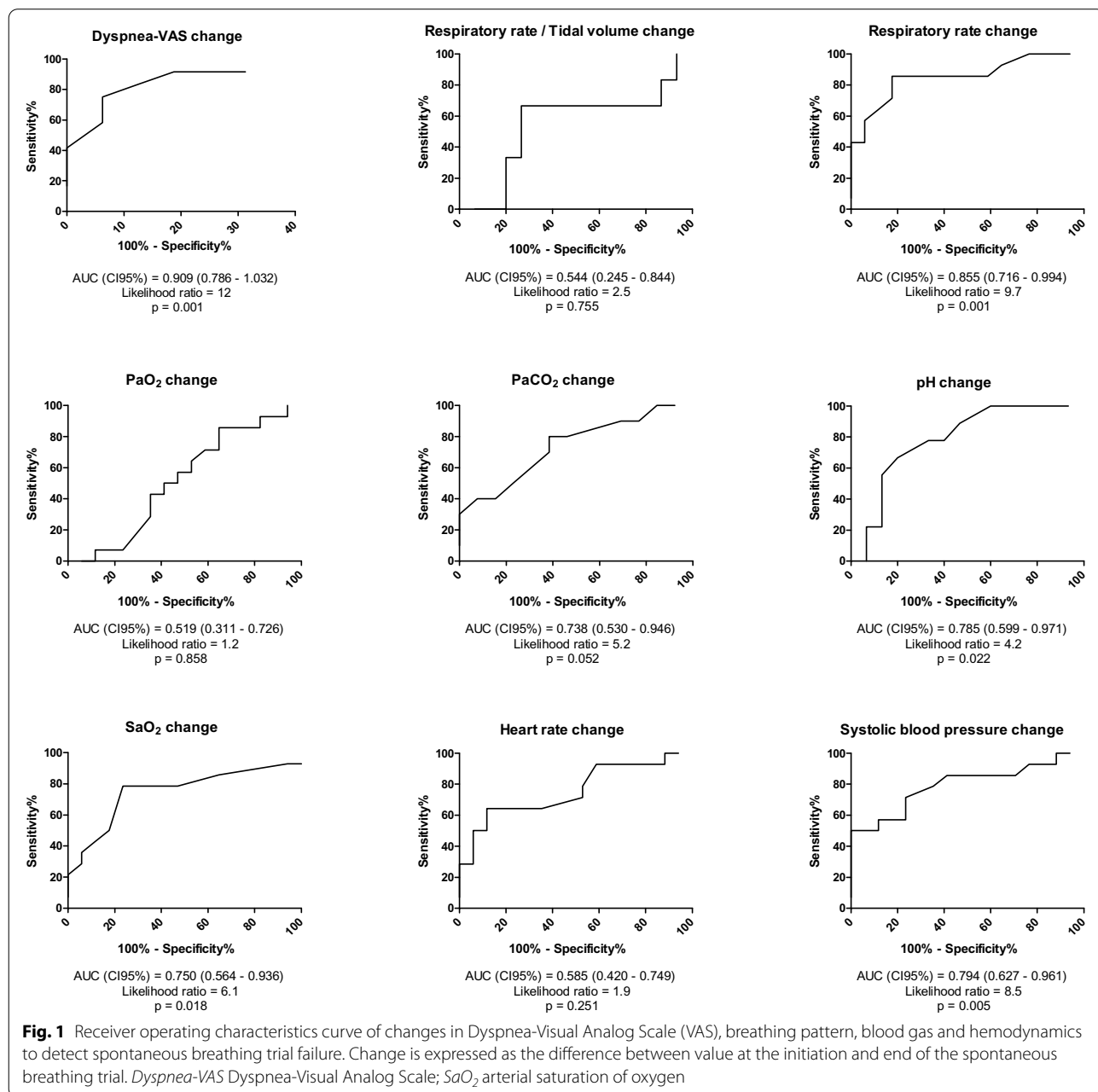


Table 4 Changes in the electromyographic activity (EMG) of the *Alae nasi*, the parasternal intercostal muscles and the diaphragm between the initiation and end of spontaneous breathing trial

	Total (n = 31)	Success (n = 17)	Failure (n = 14)	p
<i>Alae nasi</i>				
EMGmax	1.02 (0.94–1.25)	0.98 (0.77–1.10)	1.24 (0.94–1.60)	0.010
EMGauc	1.07 (0.66–1.44)	0.93 (0.60–1.11)	1.44 (0.91–2.40)	0.015
Parasternal intercostal muscles				
EMGmax	0.99 (0.87–1.01)	1.00 (0.98–1.01)	0.97 (0.83–1.01)	0.426
EMGauc	1.12 (0.90–1.69)	1.12 (1.04–1.25)	1.03 (0.71–1.78)	0.855
Diaphragm				
EMGmax	1.24 (0.80–2.06)	0.84 (0.60–1.57)	1.87 (1.19–2.92)	0.008
EMGauc	1.28 (0.98–1.81)	1.12 (0.79–1.70)	1.65 (1.47–2.93)	0.125
<i>Alae nasi</i> /diaphragm ratio				
EMGmax	0.79 (0.54–1.22)	0.87 (0.58–1.52)	0.55 (0.45–0.99)	0.039
EMGauc	0.76 (0.49–1.04)	0.72 (0.43–0.93)	0.68 (0.23–0.96)	0.812

The EMG activity is described by peak EMG (EMGmax) and area under the curve (EMGauc). Values are normalized to EMG activity at initiation of the SBT and are expressed as the ratio of the EMG activity and the end of the SBT to the EMG activity at the initiation of the SBT

Data are provided as median (interquartile range)

Dyspnea and EMG of inspiratory muscles

Changes in the EMG activity of the *Alae nasi*, parasternal intercostal muscles and diaphragm between the initiation and end of the SBT are reported in Table 4.

The change in the *Alae nasi* ($p=0.010$ for EMGmax and $p=0.015$ for EMGauc) and diaphragm ($p=0.008$ for EMGmax and $p=0.125$ for EMGauc) EMG activity between the initiation and end of the SBT was higher in patients who failed the SBT than in patients who passed. The change in parasternal intercostal EMG activity ($p=0.426$ for EMGmax and $p=0.855$ for EMGauc) was no different between patients who passed and those who failed the SBT. The contribution of extradiaphragmatic recruitment to the diaphragm ($p=0.039$ for EMGmax and $p=0.812$ for EMGauc) was lower in patients who failed the SBT than in patients who passed (Table 4). There was no correlation between extradiaphragmatic recruitment to the diaphragm and the change in dyspnea-VAS (Additional file 1: Fig. S1).

There was a significant positive correlation between the change in dyspnea-VAS between the initiation and end of the SBT and the change in the *Alae nasi* EMGauc (Rho 0.418, 95% confidence interval [CI] 0.042–0.691, $p=0.027$) (Fig. 2). There was no significant correlation between the change in dyspnea-VAS during the SBT and the change in either the parasternal EMGauc (Rho -0.121 , CI 95% -0.495 to 0.290 , $p=0.555$) or the diaphragm EMGauc (Rho 0.243, 95% CI -0.224 to 0.619 , $p=0.289$). EMGmax gave similar results (Fig. 2).

There was no significant correlation between the change in *Alae nasi* EMG activity and in parasternal EMG activity (Rho -0.016 , CI 95% -0.356 to 0.384 , $p=0.934$), between the change in *Alae nasi* EMG activity and in diaphragm EMG activity (Rho 0.308, CI 95% -0.169 to 0.669 , $p=0.186$) and between the change in parasternal EMG activity and in diaphragm EMG activity (Rho -0.047 , CI 95% -0.490 to 0.416 , $p=0.845$).

Discussion

Our results can be summarized as follows. During SBT, (1) dyspnea is a reliable criterion of weaning success and failure, suggesting that dyspnea-VAS has the potential to become a useful clinical decision-making tool for SBT; (2) dyspnea seems to be more closely related to the EMG activity of the extradiaphragmatic inspiratory muscles than to the EMG activity of the diaphragm.

Dyspnea and neural drive to breathe

These results confirm the link between increase in respiratory drive and dyspnea. Rapid increase in respiratory loading, which happens during the SBT, in turn increases the central respiratory drive to the inspiratory muscles [8]. It has been previously observed that this increase in drive involves both the diaphragm and extradiaphragmatic inspiratory muscles [19, 20]. However, extradiaphragmatic inspiratory muscles may be strongly recruited, and even more so than the diaphragm in the case of a significant increase in respiratory loading. This is the case with sternocleidomastoid muscles in patients with chronic obstructive pulmonary disease [21, 22] and mechanically ventilated critically ill patients who fail an SBT [23] and in those who fail extubation [8]. Here, we found that the increase in EMG activity of the diaphragm and the *Alae nasi* was no different, which is consistent with a recent report that showed a similar increase in the EMG of various inspiratory muscles during a progressive decrease of pressure support in mechanically ventilated patients [20].

In our study, the increase in respiratory drive was associated with an increase in dyspnea. It is of note that dyspnea was correlated with *Alae nasi* EMG activity, but not with diaphragm EMG activity. It suggests that dyspnea is more closely linked to the central respiratory drive to extradiaphragmatic inspiratory muscles than to the central respiratory drive to the diaphragm. This result is consistent with previous reports of a significant correlation between dyspnea and extradiaphragmatic inspiratory muscle EMG activity [9, 24, 25]. This result is also consistent with a recent study showing, after extubation, a small but significant correlation between dyspnea and the ultrasound thickening fraction of the parasternal

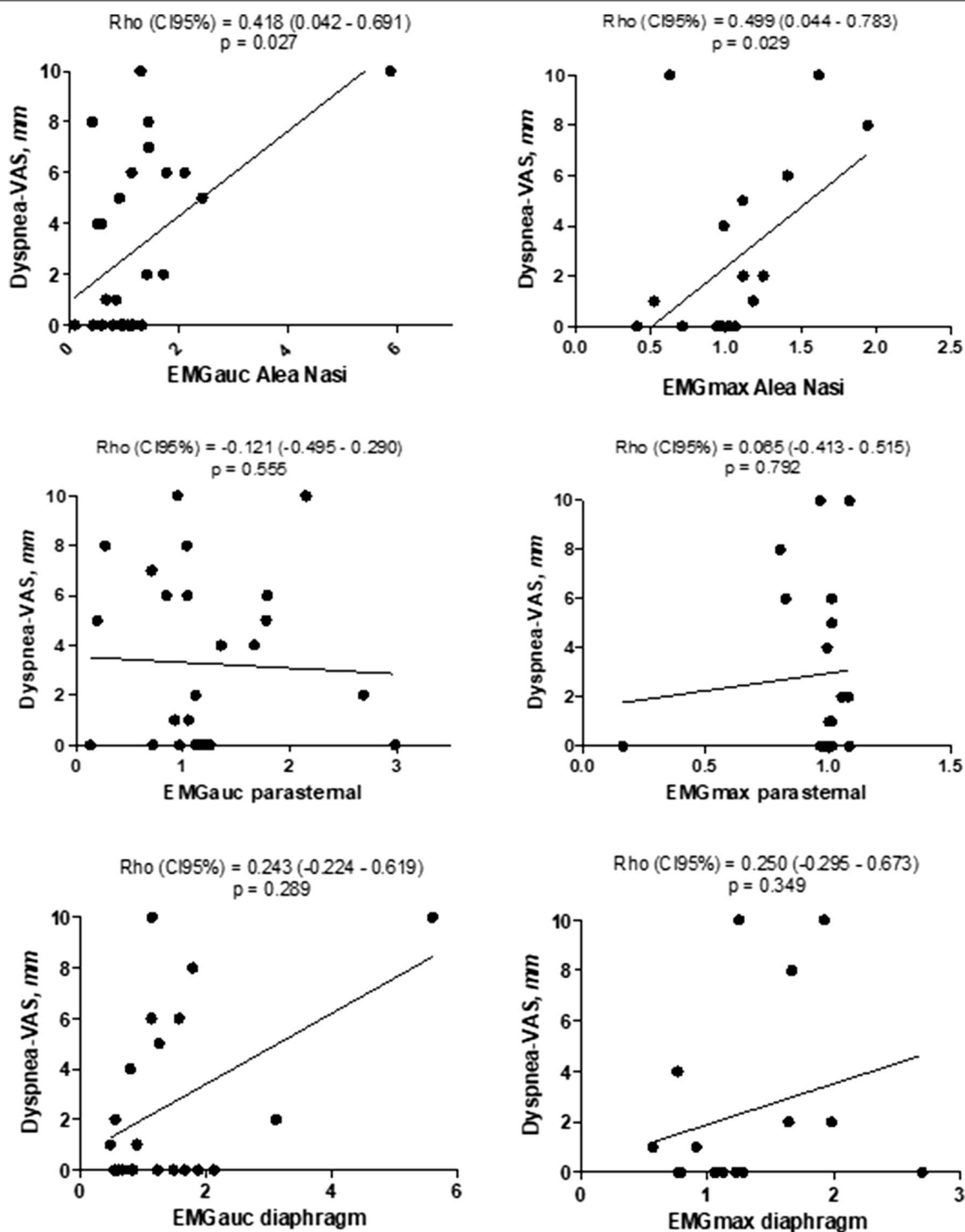


Fig. 2 Correlation between the change of Dyspnea-Visual Analog Scale (VAS) and the change in electromyographic (EMG) activity of the *Alae nasi*, parasternal intercostal muscles and diaphragm between the initiation and end of the spontaneous breathing trial. Change in dyspnea-VAS is expressed as the difference between dyspnea-VAS at the initiation and end of the spontaneous breathing trial. The EMG activity is described by area under the curve (EMGauc) and maximum (EMGmax). Values are normalized to EMG activity at initiation of the SBT and are expressed as the ratio of the EMG activity at the end of the SBT to the EMG activity at the initiation of the SBT

intercostal muscles but no significant correlation between dyspnea and the thickening fraction of the diaphragm [26].

In our study, the change in dyspnea was not correlated with the EMG of the parasternal muscle. If we cannot exclude that dyspnea is lesser closely linked to the central respiratory drive to the parasternal muscle than to the central respiratory drive to *Alae Nasi*, it is possible that this absence of correlation results from a lack of power or a technical issue.

Clinical implications: dyspnea as a monitoring tool of the SBT

Although dyspnea is a key symptom of acute respiratory failure, it is not listed among the criteria for SBT failure [1]. Our results show that dyspnea is a reliable criterion of SBT success or failure, which suggests that dyspnea-VAS could be used as a monitoring tool of the SBT rather than other variables such as heart rate, respiratory rate or arterial blood pressure. Indeed, the performance of the increase in dyspnea in detecting weaning failure seemed very good, even better than the performance of all the other variables that we tested. Our results contradict those of Haugdahl et al. who found no association between the intensity of dyspnea at the end of the SBT and the outcome of the SBT [27]. Conversely, they are compatible with those of Perren et al. who showed that, at the end of a sustained SBT, extubation success might be correlated to the patients' subjective perception of autonomous breathing [28]. In the few studies that have investigated subjective criteria during weaning [29, 30], dyspnea was significantly associated with fatigue and patients' lack of confidence in their ability to breathe without ventilatory support [29], whereas lack of dyspnea was identified as the best predictor of successful weaning [8, 30].

In our study, patients who failed the SBT reported an extremely high level of dyspnea. Dyspnea is a major cause of suffering for ICU patients, including anxiety; dyspnea could even contribute to the genesis of post-traumatic stress disorders [31, 32]. It must be stressed that relief of dyspnea is an essential clinical objective that, like pain, is currently considered by some authors to be a basic human right [33, 34]. Therefore, it is important to keep in mind that exposing ICU patients to these high levels of dyspnea during the SBT might not be without consequences.

The use of EMG, due to its technical difficulties of acquisition and interpretation, is not a suitable tool for monitoring SBT. In the present study, we used this tool to establish a relationship between dyspnea and the respective electromyographic activity (EMG) of the diaphragm and the two extradiaphragmatic inspiratory muscles.

Study limitations

This study presents limitations. First, the decision as to whether the SBT was passed or failed was based on the clinical judgment of the physician in charge of the patient; this leads to a potential inconsistency of decision criteria, even if they were based on the recommendations [1]. Second, we assessed dyspnea with only one tool, the Dyspnea-VAS. The multidimensional dyspnea profile would have provided a more detailed description of dyspnea in our patients [35]. However, this questionnaire is too long and could not be completed by patients undergoing an SBT. Third, patients were considered able to self-report dyspnea consistently if the change in the Dyspnea-VAS did not exceed 1 cm for three consecutive measurements. This led to the exclusion of several patients and limited the number of patients analyzed, but provided reliable dyspnea assessment values. Fourth, we did not measure muscle strength, only EMG as a measure of respiratory drive, and with the impossibility of making this recording reliably for several patients who had trained their exclusion. Our goal was not to assess the relationship between muscle strength and dyspnea, but rather between drive and dyspnea. Last, our work reports a longer duration of mechanical ventilation [5, 6] and a higher percentage of SBT failure [5, 6, 36] than recent studies on weaning from mechanical ventilation. Because of the small sample size and because the study was monocenter, it might be difficult to extrapolate this work. Future studies of larger sample size are needed.

Conclusion

In conclusion, during an SBT, change of dyspnea is more closely related to the EMG activity of the *Alae nasi* than to the EMG activity of the diaphragm. In addition, the intensity of dyspnea seems to be a reliable criterion of weaning success and failure. Subsequently, this suggests that change of dyspnea could be used as a simple monitoring tool of the SBT. The reliability of dyspnea in assessing SBT success now needs to be evaluated by a larger multicenter observational study.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13613-022-01025-5>.

Additional file 1: Figure S1. Correlation between the dyspnea-visual analog scale (VAS) and the PaO₂, PaCO₂, SaO₂ and respiratory rate at the initiation and the end of spontaneous breathing trial. **Figure S2.** Correlation between the change of dyspnea-visual analog scale (VAS) and the change in PaO₂, PaCO₂, SaO₂ and respiratory rate.

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Not applicable.

Author contributions

Conception and design: CB, MD, TS, AD. Data acquisition: CB, MD, TS, AD. Analysis and interpretation: CB, MD, TS, AD. Drafting the manuscript: CB, MD, TS, AD. Final approval: CB, MD, EM, JM, JD, TS, AD. All the authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Comité de Protection des Personnes Ile de France VI (No. 84-14). Informed consent was obtained from patients.

Consent for publication

Not applicable.

Competing interests

Dr. Alexandre Demoule reports personal fees from Medtronic, grants, personal fees and non-financial support from Philips, personal fees from Baxter, personal fees from Hamilton, personal fees and non-financial support from Fisher & Paykel, grants from the French Ministry of Health, personal fees from Getinge, grants and personal fees from Respinor, grants and non-financial support from Lungpacer, unrelated to the work submitted. Dr. Thomas Similowski reports, over the last 3 years, (1) personal fees from ADEP assistance, AstraZeneca France, Boehringer Ingelheim France, Chiesi France, Lungpacer Inc., Novartis France, and Vitalaire; and (2) as a member of the board of a research association, unrestricted grants from Covidien, Lungpacer, Maquet, and Philips, all unrelated to the present work. Dr. Similowski is listed as inventor on issued patents (WO2008006963A3, WO2012004534A1, WO2013164462A1) describing EEG responses to experimental and clinical dyspnea to identify and alleviate dyspnea in non-communicative patients. Dr. Côme Bureau reports personal fees from Meditor and Otsuka all unrelated to the present work. Dr. Martin Dres reports over the last three years personal fees from Lungpacer Inc., congress registration from Dräger and Research Contract with Bioserenity. Dr. Elise Morawiec, Dr. Julien Mayaux, Dr. Julie Delemazure have no competing interests related to this work.

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Dyspnea and the electromyographic activity of inspiratory muscles during weaning from mechanical ventilation

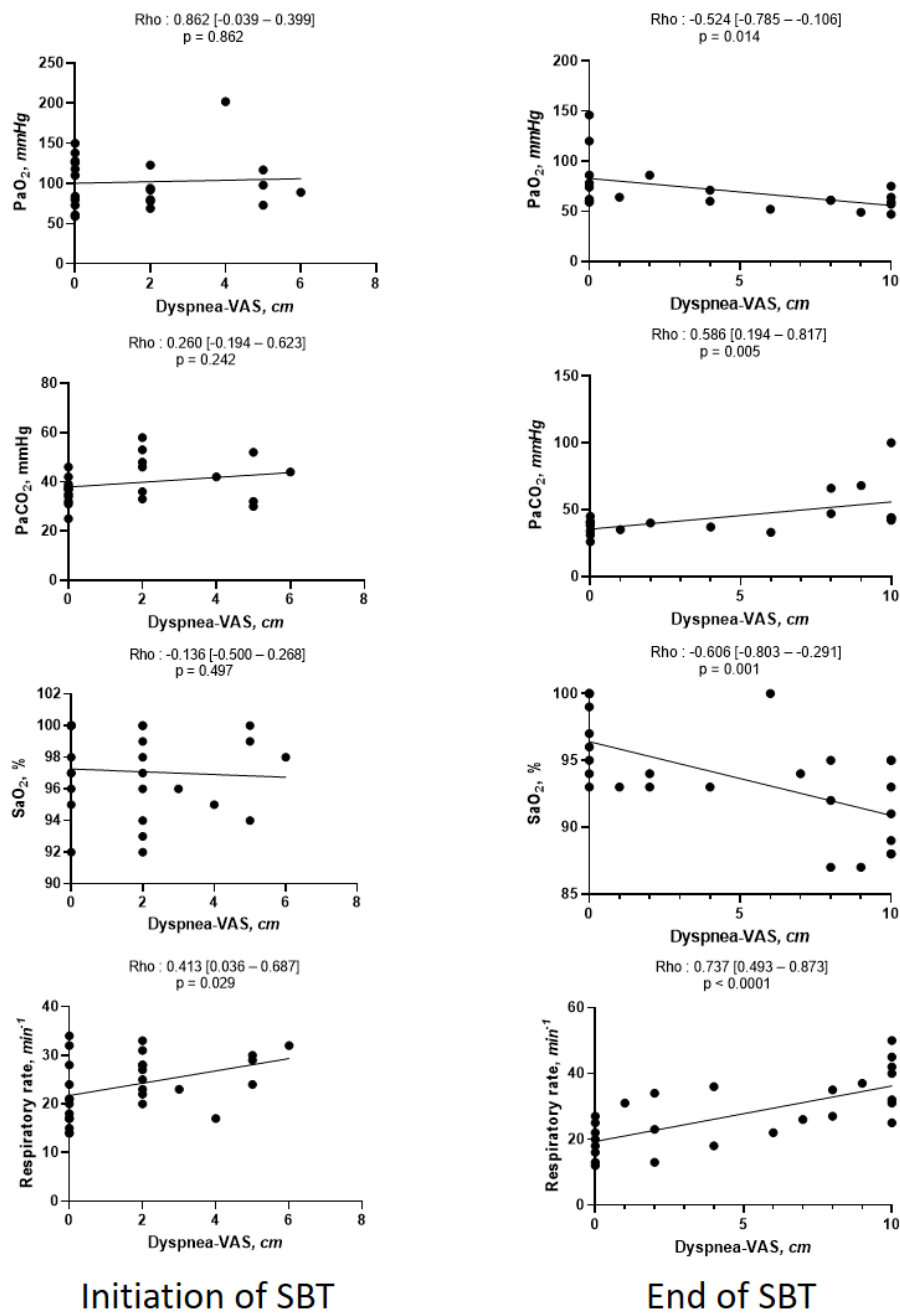
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Online Supplemental material

Figure S1. Correlation between the dyspnea-visual analog scale (VAS) and the PaO₂, PaCO₂, SaO₂ and respiratory rate at the initiation and the end of spontaneous breathing trial.

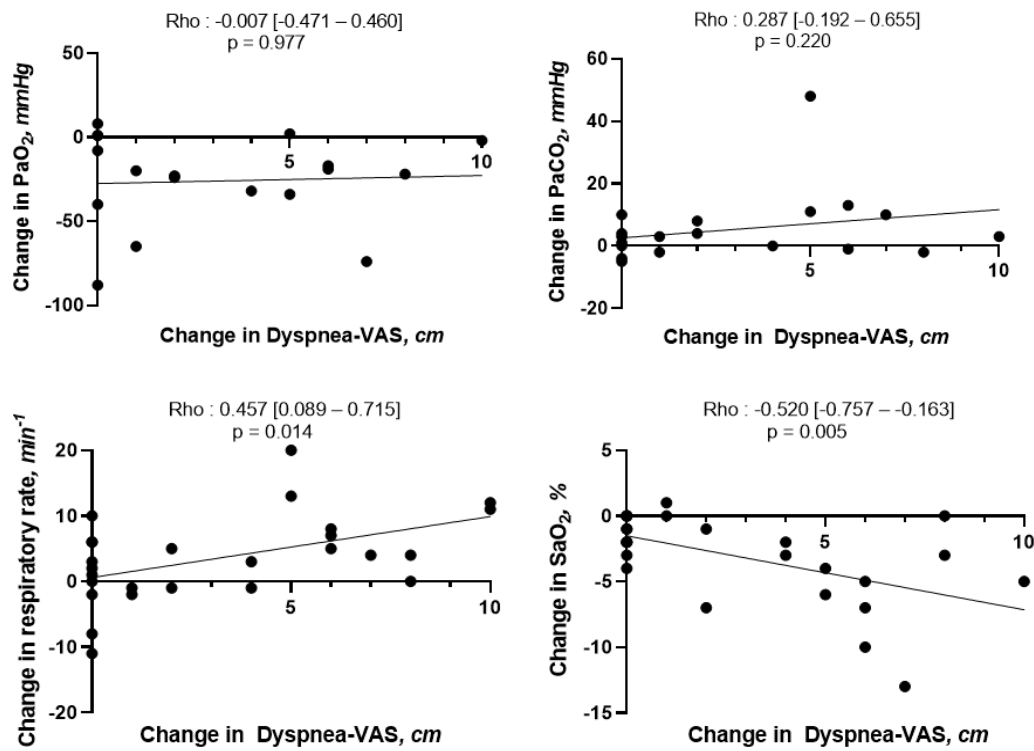
Figure S2. Correlation between the change of dyspnea-visual analog scale (VAS) and the change in PaO₂, PaCO₂, SaO₂ and respiratory rate.

Figure S1. Correlation between the dyspnea-visual analog scale (VAS) and the PaO₂, PaCO₂, SaO₂ and respiratory rate at the initiation and the end of spontaneous breathing trial.



Dyspnea-VAS, dyspnea visual analog scale

Figure S2. Correlation between the change of dyspnea-visual analog scale (VAS) and the change in PaO₂, PaCO₂, SaO₂ and respiratory rate.



Dyspnea-VAS, dyspnea visual analog scale

RESEARCH

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Proportional assist ventilation relieves clinically significant dyspnea in critically ill ventilated patients

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Abstract

Introduction: Dyspnea is common and often severe symptom in mechanically ventilated patients. Proportional assist ventilation (PAV) is an assist ventilatory mode that adjusts the level of assistance to the activity of respiratory muscles. We hypothesized that PAV reduce dyspnea compared to pressure support ventilation (PSV).

Patients and methods: Mechanically ventilated patients with clinically significant dyspnea were included. Dyspnea intensity was assessed by the Dyspnea—Visual Analog Scale (D-VAS) and the Intensive Care-Respiratory Distress Observation Scale (IC-RDOS) at inclusion (PSV-Baseline), after personalization of ventilator settings in order to minimize dyspnea (PSV-Personalization), and after switch to PAV. Respiratory drive was assessed by record of electromyographic activity of inspiratory muscles, the proportion of asynchrony was analyzed.

Results: Thirty-four patients were included (73% males, median age of 66 [57–77] years). The D-VAS score was lower with PSV-Personalization (37 mm [20–55]) and PAV (31 mm [14–45]) than with PSV-Baseline (62 mm [28–76]) ($p < 0.05$). The IC-RDOS score was lower with PAV (4.2 [2.4–4.7]) and PSV-Personalization (4.4 [2.4–4.9]) than with PSV-Baseline (4.8 [4.1–6.5]) ($p < 0.05$). The electromyographic activity of parasternal intercostal muscles was lower with PAV and PSV-Personalization than with PSV-Baseline. The asynchrony index was lower with PAV (0% [0–0.55]) than with PSV-Baseline and PSV-Personalization (0.68% [0–2.28] and 0.60% [0.31–1.41], respectively) ($p < 0.05$).

Conclusion: In mechanically ventilated patients exhibiting clinically significant dyspnea with PSV, personalization of PSV settings and PAV results in not different decreased dyspnea and activity of muscles to a similar degree, even though PAV was able to reduce asynchrony more effectively.

Keywords: Mechanical ventilation, Dyspnea, Clinical study, Physiology

Introduction

Dyspnea is one of the most distressing sensations experienced by critically ill patients [1]. It is estimated that one-half of intubated patients experience dyspnea, which is responsible for immediate suffering and a poorer prognosis [2]. Relief of dyspnea is a priority in these patients

[3]. Dyspnea in mechanically ventilated patients is partly due to a mismatch between the patient's inspiratory effort and the level of assistance, corresponding to under-assistance [2]. This mismatch may also generate patient-ventilator asynchrony, which is associated with poorer clinical outcomes [4].

With pressure support ventilation (PSV), the most widely used mode of partial ventilatory assistance, a constant preset level of pressure assists each inspiration regardless of the patient's inspiratory effort. A mismatch between the patient's inspiratory effort and the level of

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assistance is therefore likely to occur [2, 5–11]. Ventilator settings such as the assist control mode and a low pressure support level are associated with increased dyspnea [2, 12]. Proportional assist ventilation (PAV) is a mode of mechanical ventilation that adjusts the level of assistance to the intensity of respiratory muscle activity. As opposed to PSV, PAV+ adjusts the level of assistance in real time to the patient's inspiratory effort, which in turn prevents under-assistance and over-assistance [13–18]. Few data are currently available concerning the impact of PAV+ on dyspnea, as most studies have been conducted in healthy subjects or ICU patients without clinically significant dyspnea [13–17, 19–21].

Our first hypothesis was that PAV+ would be more effective than PSV with personalized settings to relieve clinically significant dyspnea. We also hypothesized that this beneficial effect of PAV+ on dyspnea would be associated with decreased respiratory drive, a major determinant of dyspnea [22] and increased variability of the breathing pattern, a marker of adequate load–capacity balance [7, 9–11, 17, 19, 20, 23]. Finally, we sought to evaluate the respective impact of PAV+ and personalized PSV settings on patient–ventilator asynchrony. We therefore compared the respective impacts of PSV with personalized ventilator settings and PAV+ on dyspnea in mechanically ventilated patients exhibiting clinically significant dyspnea.

Patients and methods

This, single-center prospective study was performed over a 7-month period in the 10-bed Medical ICU of the Respiratory and ICU Division of La Pitié-Salpêtrière hospital, Paris, France.

Patients

The study was approved by the *Comité de Protection des Personnes Ile de France VI* (No. 125-15). Informed consent was obtained from patients or relatives.

Patients were eligible when they met the following criteria: (1) intubation and mechanical ventilation for more than 24 h, for a respiratory cause with hypoxemia defined as a $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg recorded at least once; (2) PSV ventilation for > 6 h; (3) clinically significant dyspnea, defined in communicative patients by a dyspnea visual analog scale (D-VAS, bounded on the left by “no respiratory discomfort” and on the right by “intolerable respiratory discomfort”) ≥ 40 on a scale from 0 to 100 or an Intensive Care-Respiratory Distress Operating Scale (IC-RDOS, see below) score ≥ 2.4 [2], and in non-communicative patients by an IC-RDOS score ≥ 2.4 ; (4) decision of the physician in charge of the patient to evaluate PAV+ after personalization of ventilator settings; (5) Richmond Agitation and Sedation Scale (RASS) between

– 2 and + 2 and Glasgow Coma Scale > 12 . Patients were considered communicative when they were able to consistently self-report dyspnea, as attested by a D-VAS variation not exceeding 10 mm for three consecutive measures [11, 24, 25].

Exclusion criteria were: (1) severe hypoxemia defined as a $\text{PaO}_2/\text{FiO}_2$ ratio < 150 mmHg; (2) delirium according to the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU); (3) hemodynamic instability defined by the need for intravenous volume expansion or vasopressors during the previous 24 h; (4) age < 18 years, known pregnancy, protected adult; (5) brain damage defined by Glasgow Coma Scale < 9 and (6) neuromuscular disease.

Measurements

Anthropometric data, medical history and current treatments were collected at inclusion.

Quantification of dyspnea

Dyspnea measurements were performed in the presence of two experimenters who were not the physicians in charge of the patients. Dyspnea was quantified in all patients by means of the IC-RDOS, which is an observational dyspnea scale based on five physical and observable signs of respiratory distress (heart rate, use of neck muscles during inspiration, abdominal paradox, facial expression of fear, supplemental oxygen) tailored to best correlate with D-VAS in communicative ICU patients [26]. In addition, in communicative patients only, dyspnea was also quantified by placing a cursor on a 10-cm D-VAS.

Airway pressure and flow

Airway flow was measured with a pneumotachograph (Hans Rudolph, Kansas City, USA) inserted between the Y-piece and the endotracheal tube before being connected to a differential pressure transducer (Validyne, Northridge, USA). Airway pressure was measured at the Y-piece by a differential pressure transducer (Validyne, Northridge, USA).

Electromyography (EMG) of extradiaphragmatic inspiratory muscles

The amplitude of the extradiaphragmatic inspiratory muscle EMG signal is a surrogate for central respiratory drive and is proportional to dyspnea intensity [27]. The EMG signal was collected by self-adhesive surface electrodes like those commonly used to record the electrocardiogram signal in critically ill patients, with an interval of 2 cm between the two electrodes. Electrode positions varied according to the muscle recorded. For EMG of the parasternal intercostal muscles, electrodes

were placed next to the second intercostal space as close as possible to the sternum. For EMG of the alae nasi muscles, electrodes were placed on the lateral surfaces of the nose (nostrils) [12]. EMG signals were amplified, sampled at a frequency of 10 kHz, filtered between 40 and 500 Hz (PowerLab, AD Instruments, Hastings, UK) and the root-mean-squared electromyogram was calculated [12, 28] (see Additional file 1: method, detailed measurement of electromyography of extradiaphragmatic inspiratory muscles).

Arterial blood gases

Blood gases were sampled at the end of each condition using an arterial catheter.

Study design

Patients were mechanically ventilated by a PB 840 ventilator (Medtronic, Boulder, USA). Three successive conditions were studied. Changes in settings were decided by the physician in charge of the patient.

The first condition was defined as "PSV-Baseline" and corresponded to the settings used at the time of inclusion by the physician in charge. These ventilator settings were those observed on the ventilator when significant dyspnea was detected. The second condition was defined as "PSV-Personalization" and consisted in personalization of PSV settings left to the discretion of the physician in charge of the patient in order to reduce clinically significant dyspnea. Ventilator adjustments were applied to at least one setting among pressure support level, cycling-off and inspiratory trigger. Briefly, the level of pressure support was increased and the level of expiratory trigger was decreased in order to increase the level of assistance without generating a tidal volume greater than 10 mL/kg or inducing ineffective triggering, corresponding to asynchrony that is known to be associated with over-assistance [29, 30]. The third condition was defined as "PAV". The patient was first switched to the PAV+ mode. As recommended by local guidelines with this mode, the level of assistance, referred to as assistance percentage or gain, was set to maintain the patient at a respiratory effort target corresponding to a muscle pressure-time product (PTP_{mus}) between 50 and 150 cmH₂O·s·min⁻¹. As it was not possible to directly calculate PTP_{mus} at the bedside, we analyzed the maximum inspiratory muscle pressure, considering it to be the main component of PTP_{mus}, as previously reported [31]. The peak respiratory muscle pressure was estimated as (peak airway pressure – positive end-expiratory pressure (PEEP) × ((100 – gain)/gain)). A grid constructed from this equation provided a quick estimation of the peak respiratory muscle pressure at the bedside, which was maintained between 5 and 10

cmH₂O [31] (see Additional file 1: Method, Algorithm for PAV+ adjustment).

Each patient underwent three 30-min trials under each condition, consisting of a 20-min initial stabilization period followed by a 10-min recording. The endotracheal tube was suctioned before starting each recording. PEEP and FiO₂ were maintained constant throughout the study period at the values used before patient enrolment.

Data analysis

Breathing pattern and breath-by-breath variability

Breathing pattern variables were determined on a breath-by-breath basis for each of the three conditions (Labchart 7.3[®] software, ADInstruments, Dunedin, New Zealand). These included respiratory rate (RR), tidal volume (V_T), inspiratory time (Ti), and maximal inspiratory pressure (P_{max}). The coefficient of variation for RR, V_T, Ti, and P_{max} were calculated as the ratio of the standard derivation to the mean.

Detection and quantification of patient-ventilator asynchrony

The three most common observed forms of patient-ventilator asynchrony were quantified on the basis of flow and pressure on the 10-min recording performed in each condition [32]. Ineffective triggering (IT) was defined as an airway pressure drop >0.5 cmH₂O or flow elevation not followed by a ventilatory cycle. Double triggering (DT) was defined as the presence of two ventilatory cycles separated by a very short expiratory time. Auto-triggering (AT) was defined as a ventilatory cycle without a prior pressure drop [13]. The asynchrony index (AI) was defined as ((AT + IT + DT)/total respiratory rate) × 100; total respiratory rate was defined as [IT + respiratory rate] [13] (see Additional file 1: Method S3. Quantification of patient-ventilator asynchrony).

Electromyogram (EMG) of extradiaphragmatic inspiratory muscles

Inspiratory muscle EMG activity, used to estimate respiratory drive, was processed using the Labchart Peak Analysis module MLS380/8 (ADInstruments, Dunedin, New Zealand). This module generated a root mean square of the EMG smoothed over 1-s fixed windows that was used to measure the maximum amplitude of the EMG signal (EMG_{max}), defined by the difference between the maximum amplitude of the root mean square signal (RMS) and its baseline, and the area under the EMG signal curve (EMG_{auc}), calculated by integration of the RMS between its deflection from the baseline and its return to this same baseline time-locked on a respiratory cycle [28]. EMG_{max} and EMG_{auc} were expressed as a proportion of the activity measured under the "PSV-Baseline" condition

in order to normalize the values due to the variability of skin impedance and patient's morphology.

Statistical analysis

Statistical analysis was performed with Prism 8.0 software (GraphPad Software, USA). Kolmogorov–Smirnov test was used to assess normality of data distribution. Quantitative variables were described by their median and interquartile interval. Qualitative variables were expressed in absolute value and percentage. All analyses were performed with a type I error of 5%. Results were compared between the following conditions: PSV-Baseline, PSV-Personalization and PAV. Discrete variables were compared by Chi-square test. Continuous variables were compared using a Friedman test, followed, when positive, by a post hoc comparison using a Dunn multiple comparison test. Correlations between variables were evaluated using the Spearman rank correlation coefficient.

Considering a power of 80% and standard deviations of 3 for IC-RDOS and 10% for the patient–ventilator asynchrony index, we calculated a sample size of at least 28 patients for this study. As we expected that PSV-Personalization or PAV could not be achieved in 20% of patients, we increased sample size to 34 patients.

Results

Ninety-five patients with invasive mechanical ventilation and dyspnea were admitted during the period. One patient was under 18 years, six with RASS + 2, 19 refused to participate, for 35 a technical reason (equipment failure, weekend) could not allow inclusion.

Thirty-four patients were included. Patient characteristics are shown in Table 1. Thirty-three patients were connected to the ventilator using an endotracheal tube, while one patient was connected using a tracheostomy tube. The three conditions were studied in all patients. Eight patients were still receiving sedation at the time of inclusion, they were all receiving sufentanil at a dose of 5 µg/h. Ventilator settings in each of the three conditions are reported in Table 2. Personalization consisted in decreasing the inspiratory trigger for 13 patients (38%), increasing the pressure support level for all patients and decreasing the cycling-off for 18 patients (53%). Compared to PSV-Baseline, pressure support level was higher and cycling-off level was lower after personalization of ventilator settings. FiO₂ and PEEP were not significantly different across the three conditions.

Dyspnea and extradiaphragmatic inspiratory muscle EMG activity

D-VAS scores for communicative patients and IC-RDOS scores for all patients in the three conditions are shown

Table 1 Characteristics of the study population

<i>Demographic characteristics</i>	
Gender, male	25 (73)
Age, year	66 (57–77)
Weight, kg	75 (64–91)
Height, m	1.72 (1.61–1.78)
Body mass index, kg m ⁻²	26 (22–29)
Duration of mechanical ventilation prior to inclusion, days	6 (4–9)
Duration of mechanical ventilation after inclusion, days	3 (2–3)
At least one spontaneous breathing trial performed before enrolment, n (%)	7 (21)
Sedation on inclusion, n (%)	8 (23)
RASS	0.0 (-0.7–1.0)
<i>Comorbidities</i>	
Chronic respiratory disease, n (%)	14 (41)
Chronic heart failure, n (%)	2 (6)
<i>Reason for intubation</i>	
Bacterial pneumonia, n (%)	11 (33)
Viral or fungal pneumonia, n (%)	4 (12)
Aspiration pneumonia, n (%)	3 (9)
Acute on chronic respiratory failure, n (%)	10 (30)
Cardiogenic pulmonary edema, n (%)	2 (6)
Other, n (%)	4 (12)
<i>Severity scores</i>	
SAPS at admission	56 (38–66)
SOFA at inclusion	6 (4–9)

RASS Richmond Agitation and Sedation Scale, SAPS Simplified Acute Physiology Score, SOFA Sepsis-related Organ Failure Assessment

Data are expressed as median (interquartile range) and number (%)

in Fig. 1. D-VAS could not be rated in 16 patients due to hearing impairment ($n=3$), language barriers ($n=4$); ongoing sedation ($n=4$) and misunderstanding of the instructions ($n=5$). D-VAS was therefore available in 18 patients. D-VAS was lower with PSV-Personalization (37 [20–55], $p=0.001$) and PAV (31 [14–45], $p=0.001$) than with PSV-Baseline (62 [28–76], $p=0.001$ for both). There was no significant difference in terms of D-VAS between PSV-Personalization and PAV. IC-RDOS was measured in all patients. IC-RDOS was lower with PAV (4.18 [2.36–4.71]) than with PSV-Baseline (4.76 [4.11–6.46], $p=0.002$), but there was no significant difference with PSV-Personalization (4.35 [2.39–4.92]). There was no significant difference between PSV-Personalization and PAV. The results are expressed as differences between the conditions in Additional file 1: Table S1.

In communicative patients ($n=18$) there was a significant positive correlation between D-VAS and IC-RDOS with PSV-Personalization ($Rho=0.54$ [0.07–0.81], $p=0.02$), but there was no significant correlation with PSV-Baseline ($Rho=0.41$ [– 0.10 to

Table 2 Ventilator settings at baseline (PSV-Baseline), after personalization of ventilator settings (PSV-Personalization) and with proportional assist ventilation (PAV)

	PSV-Baseline	PSV-Personalization	PAV
FiO ₂ , %	30 (30–40)	30 (30–40)	30 (30–40)
PEEP, cmH ₂ O	5 (5–6)	5 (5–6)	5 (5–6)
Pressure support level, cmH ₂ O	6 (6–8)	14 (14–16)*	–
Inspiratory trigger, L/min	1 (1–2)	1 (1–1)	–
Cycling off, %	30 (25–30)	20 (15–29)*	–
Percentage assist, %	–	–	70 (70–80)
Flow sensitivity, L/min	–	–	2.0 (1.5–2.0)
Expiratory sensitivity, L/min	–	–	2 (1–2)

FiO₂ inspired oxygen fraction, PEEP positive end-expiratory pressure

Data are expressed as median (interquartile range) and number (%)

*p < 0.05 as compared to PSV-Baseline

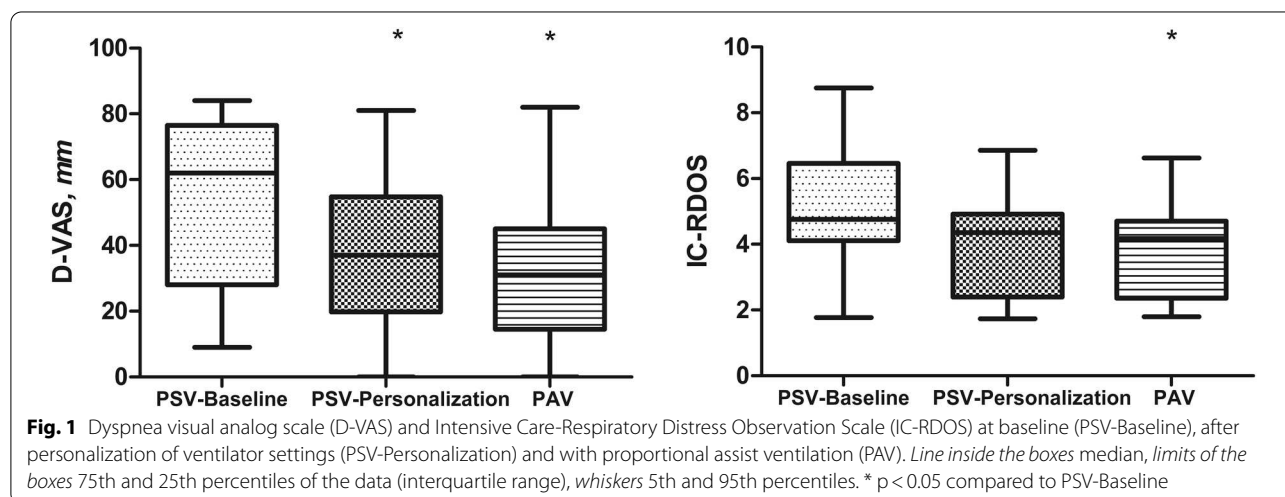


Fig. 1 Dyspnea visual analog scale (D-VAS) and Intensive Care-Respiratory Distress Observation Scale (IC-RDOS) at baseline (PSV-Baseline), after personalization of ventilator settings (PSV-Personalization) and with proportional assist ventilation (PAV). Line inside the boxes median, limits of the boxes 75th and 25th percentiles of the data (interquartile range), whiskers 5th and 95th percentiles. * p < 0.05 compared to PSV-Baseline

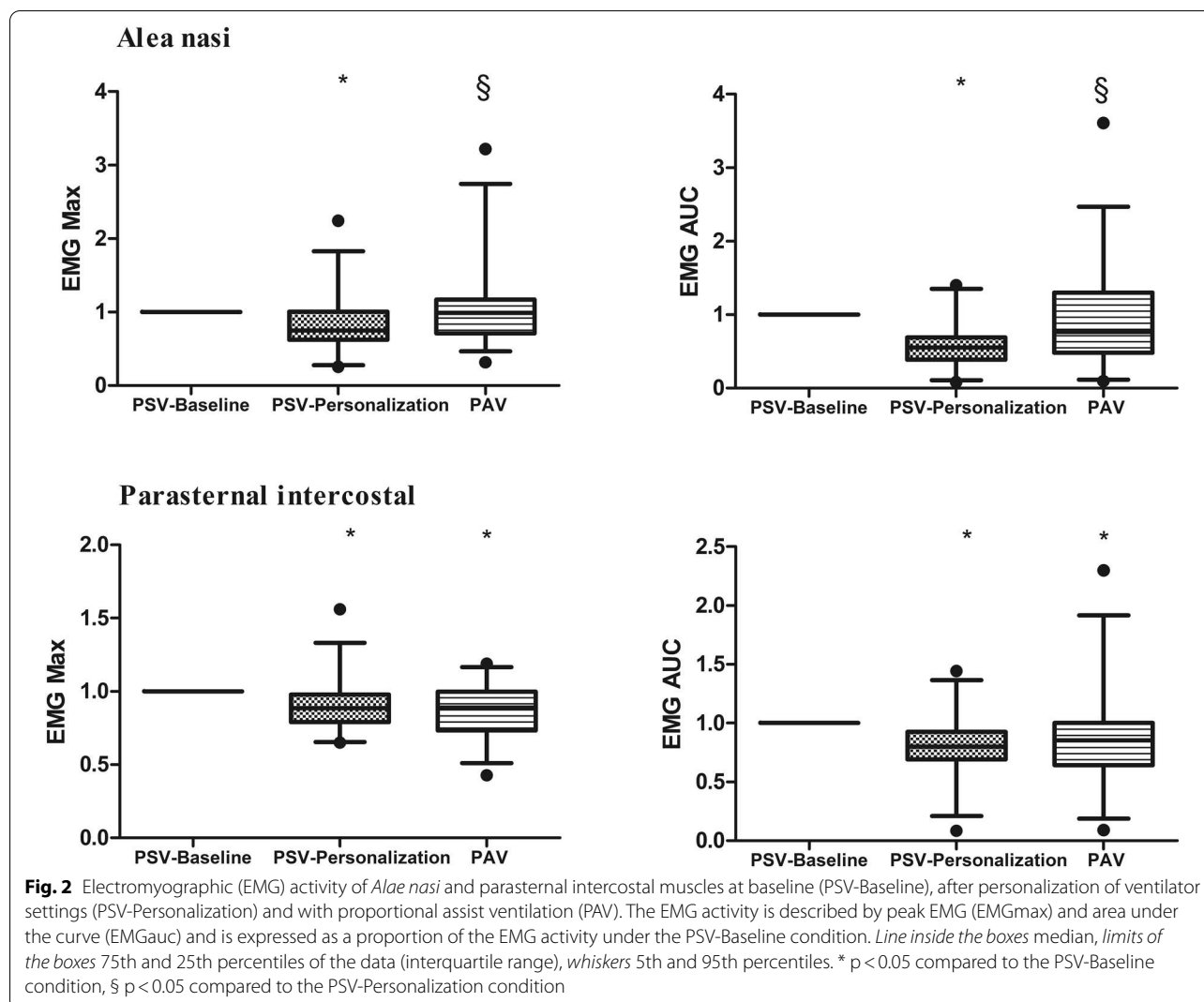
0.75], $p=0.10$) and PAV (Rho=0.44 [– 0.06 to 0.77], $p=0.07$) (see Additional file 1: Figure S1).

There was a significant negative correlation between D-VAS and the coefficient of variation of RR (Rho= – 0.29 [– 0.52 to – 0.02], $p=0.031$) (see Additional file 1: Figure S2). There was a significant negative correlation between IC-RDOS and the coefficient of variation of RR (Rho= – 0.43 [– 0.58 to – 0.26], $p<0.0001$), V_T (Rho= – 0.33 [– 0.50 to – 0.15], $p=0.001$), T_i (Rho= – 0.22 [– 0.40 to – 0.02], $p=0.025$) and P_{max} (Rho= – 0.33 [– 0.50 to – 0.14], $p=0.001$).

There was a significant negative correlation between IC-RDOS and the pH in PSV (Rho= – 0.51 [– 0.71 to – 0.24], $p=0.001$), but there was no correlation in PAV (Rho= – 0.29 [– 0.66 to – 0.19], $p=0.221$). There was no correlation between IC-RDOS and

bicarbonatemia in PSV (Rho= – 0.14 [– 0.43 to 0.18], $p=0.371$) or in PAV (Rho= – 0.08 [– 0.52 to 0.39], $p=0.734$) (Additional file 1: Figure S3).

EMG activity of the *Alae nasi* and parasternal intercostal muscles in the three conditions is shown in Fig. 2. Compared to PSV-Baseline, *Alae nasi* EMG activity was lower with PSV-Personalization ($p=0.008$). *Alae nasi* EMG activity was higher with PAV than with PSV-Personalization, but there was no significant difference in terms of *Alae nasi* EMG activity between PSV-Baseline and PAV. Compared to PSV-Baseline, parasternal intercostal muscle EMG activity was lower with PSV-Personalization and PAV ($p=0.001$). There was no significant difference in terms of parasternal intercostal EMG activity between PSV-Personalization and PAV.



Breathing pattern, breath-by-breath variability, and blood gases

Breathing pattern, coefficients of variation and blood gases are shown in Table 3. Compared to PSV-Baseline, PSV-Personalization of ventilator settings resulted in a decrease of RR and an increase of T_i , V_T and V_T/T_i . Compared to PSV-Personalization, PAV resulted in an even lower RR, higher T_i , and lower V_T/T_i .

The coefficients of variation of RR, V_T , and P_{max} were higher with PAV than with PSV-Baseline and PSV-Personalization.

pH was lower with PSV-Personalization and PAV than with PSV-Baseline. PaO_2 was higher with PAV than with PSV-Baseline and $PaCO_2$ was lower with PSV-Personalization than with PSV-Baseline.

The results are expressed as differences between the conditions in Table S1.

Patient-ventilator asynchrony

The AI under the three conditions is shown in Fig. 3. There was no significant difference between the AI with PSV-Baseline (0.68 [0–2.28]%) and PSV-Personalization (0.60 [0.31–1.41]%). The AI was lower with PAV (0 [0–0.55]%) than with PSV-Baseline ($p = 0.001$) and PSV-Personalization ($p = 0.001$). There was no correlation between the AI and dyspnea assessed by IC-RDOS (Rho = 0.05 [– 0.16 to 0.25], $p = 0.622$) (Fig. 3). The decreased prevalence of double triggering accounted for most of the reduction of AI observed with PAV, as PAV was not associated with a decrease of the prevalence of auto-triggering or ineffective triggering (see Additional file 1: Figure S4). There was no correlation between the double triggering prevalence and dyspnea assessed by IC-RDOS (Rho = 0.01 [– 0.20 to 0.21], $p = 0.953$) (see Additional file 1: Figure S5).

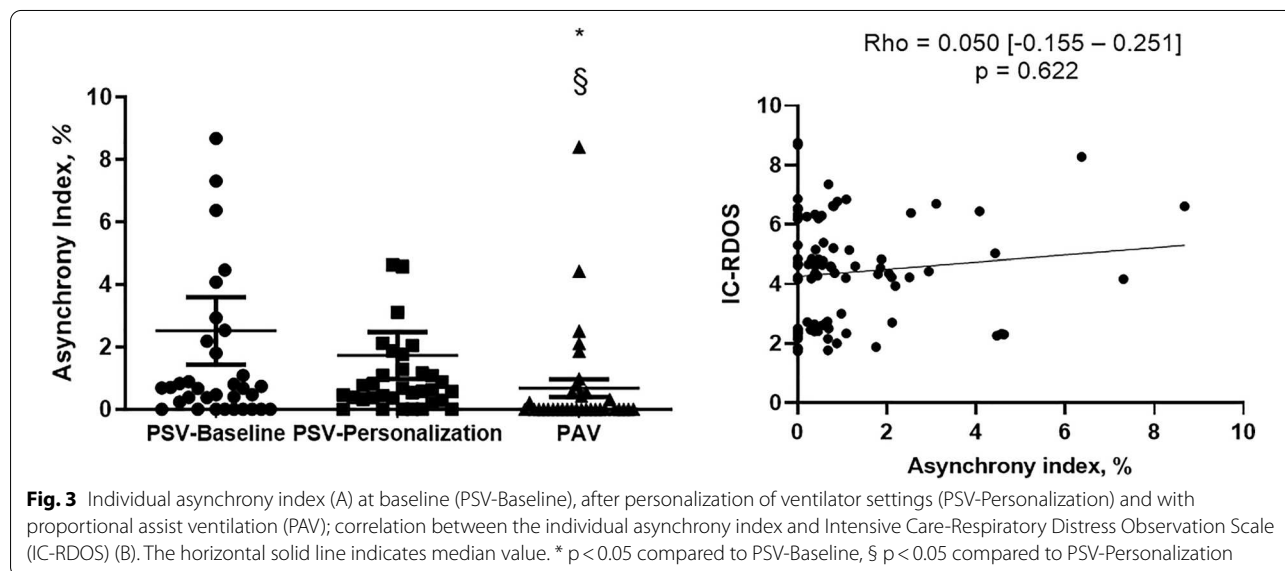
Table 3 Breathing pattern and blood gases at baseline (PSV-Baseline), after personalization of ventilator settings (PSV-Personalization) and with proportional assist ventilation (PAV)

	PSV-Baseline	PSV-Personalization	PAV	p
<i>Breathing pattern</i>				
RR, min ⁻¹	27 (22–32)	24 (20–30)*	21 (17–28)*§	<0.0001
V _T , ml/kg IBW	7.0 (5.6–9.7)	7.8 (7.0–9.8)*	9.0 (6.5–10.5)*	<0.0001
T _i , sec	0.75 (0.61–0.95)	0.85 (0.67–1.03)	0.97 (0.82–1.27)*§	<0.0001
V _T /T _i , L/s ⁻¹	1.15 (0.74–1.55)	1.97 (1.23–3.16)*	0.84 (0.62–1.06)§	<0.0001
P _{max} , cmH ₂ O	13 (12–15)	21 (18–23)*	24 (19–29)*	<0.0001
EtCO ₂ , mmHg	33 (28–38)	31 (26–35)	31 (27–37)	0.033
<i>Breath-by-breath variability</i>				
CV RR, %	13 (10–20)	14 (11–24)	22 (15–28)* §	0.001
CV V _T , %	15 (11–20)	15 (10–26)	25 (17–43)* §	<0.001
CV T _i , %	22 (16–43)	33 (19–50)	22 (13–27) §	0.023
CV V _T /T _i , %	23 (16–39)	29 (15–42)	23 (14–60)	0.632
CV P _{max} , %	4 (4–06)	6 (3–10)	16 (11–23)* §	<0.001
<i>Blood gases</i>				
pH	7.43 (7.36–7.44)	7.41 (7.39–7.47)*	7.42 (7.37–7.48)*	0.012
PaO ₂ , mmHg	80 (73–99)	87 (73–101)	88 (79–98)*	0.016
PaCO ₂ , mmHg	41 (36–49)	39 (34–47)*	39 (33–48)	0.001
SaO ₂ , %	96 (94–98)	96 (94–98)	97 (96–98)	0.038
HCO ₃ ⁻ , mmol/L	26.6 (22.7–28.9)	26.8 (22.7–29.4)	26.9 (22.1–28.6)	0.503
A-aO ₂ gradient, mmHg	94 (72–154)	96 (85–158)	82 (64–143) §	0.023

RR respiratory rate, T_i inspiratory time, V_T tidal volume, IBW ideal body weight, EtCO₂ CO₂ expired fraction, CV coefficient of variation, P_{max} peak airway pressure, A-aO₂ Gradient, alveolar–arterial oxygen gradient

Data are expressed as median (interquartile range) and number (%)

* p < 0.05 compared to the PSV-Baseline condition; § p < 0.05 compared to the PSV-Personalization condition



Discussion

Our results can be summarized as follows. In patients with clinically significant dyspnea: (1) PAV + and personalized PSV settings relieved dyspnea; (2) PAV + and

personalized PSV settings seemed not to have a different impact on dyspnea and respiratory drive, as assessed by respiratory muscle EMG activity; (3) breath-by-breath variability was higher with PAV + and was inversely

correlated with dyspnea; (4) PAV+ was more effective than personalized PSV settings to reduce patient–ventilator asynchrony. To our knowledge, this is the first study to compare personalized PSV settings and PAV+ in mechanically ventilated patients exhibiting clinically significant dyspnea. In this study, we confirm that simple changes in ventilator settings can suffice to achieve a spectacular effect on dyspnea [2]. In addition, we have increased the panel of possible changes of ventilator settings by adding another option, which is switching to PAV+.

Dyspnea, variability, load–capacity balance and neural drive to breathe

Our results suggest that improvement of dyspnea resulted from a reduction of respiratory loading, which in turn reduced the intensity of respiratory drive, as illustrated by the decreased amplitude of the parasternal intercostal and *alae nasi* EMG activities, two surrogates for central respiratory drive. These findings are in complete agreement with previous studies reporting a close correlation between dyspnea and respiratory drive in mechanically ventilated patients, and a cortical contribution to the drive to breathe in dyspneic MV patients [12, 33]. Improvement of dyspnea was associated with a concomitant increase in V_T , which raises an issue regarding protective mechanical ventilation with low V_T in patients able to perceive dyspnea. Indeed, low V_T is recommended for adequate lung protection, but seems to be associated with more severe respiratory suffering [7]. The increase in breath-by-breath variability is another argument in favor of reduction of respiratory loading with PAV+. In awake normal humans, breath-to-breath variability tends to decrease in response to mechanical loading [34]. During weaning from mechanical ventilation, an inverse relationship between the breath-to-breath variability of V_T/T_i and dynamic compliance of the respiratory system has been reported [35]. In contrast, unloading of the respiratory system with increasing levels of assistance increases breath-by-breath variability [36]. The load–capacity relationship of the respiratory system is therefore a major determinant of breath-to-breath variability: the higher the loading, the lower the variability. However, the higher breath-by-breath variability observed with PAV+ may also be due to the proportionality of the assistance that “unmasks” the underlying variability in central respiratory neural output [36]. In other words, PAV+ reveals the natural fluctuations in the resting breathing pattern of humans that appear to originate from the activity of central pattern generators [37]. This proportional ventilation, which tends to preserve the natural variability of breathing, may also explain why PAV+ is slightly more beneficial on dyspnea. To the best of our knowledge, this is the

first report of an inverse correlation between dyspnea and breath-by-breath variability.

Patient–ventilator asynchrony

While personalized PSV failed to decrease patient–ventilator asynchrony, PAV+ significantly decreased the prevalence of asynchrony and, more specifically, the prevalence of double triggering [38], a pattern of asynchrony that may increase tidal volume and consequently expose the lung to overdistension and subsequent ventilator-induced lung injury [39, 40]. In addition, double triggering is a form of asynchrony that occurs when the level of assistance is too low and does not meet a high respiratory drive [32]. The reduction of double triggering provides further evidence that PAV+ is associated with a better load–capacity balance.

Clinical implications

Although PAV+ and personalized PSV were equally effective on dyspnea, it should be stressed that they are not equally time-consuming. On the one hand, personalization of PSV is very time-consuming, as it requires regular assessment of the breathing pattern to better adapt ventilator settings. On the other hand, PAV+ constantly adapts the level of assistance delivered by the ventilator to the patient’s inspiratory muscle activity, without any human intervention. Indeed, in a study that evaluated to what extent mechanical ventilation with PAV+ could keep patients in a comfort zone for several days, the median daily number of load-adjustable gain factors was one [31]. The fact that PAV+ was more effective than PSV to reduce the prevalence of patient–ventilator asynchrony is another argument supporting a potential benefit of PAV+, as asynchrony is associated with prolonged duration of mechanical ventilation and even high mortality [4, 41].

Strengths and limitations of the study

A major strength of our study is that it compared PAV+ delivered according to a standard protocol to PSV with improved settings. In previous studies comparing PAV+ and PSV, PSV was delivered in the absence of any precise guidelines and it was therefore difficult to conclude whether the benefit of PAV+ was actually due to superiority of this mode of ventilation per se or to poorly personalized PSV settings. In addition, PAV+ was also delivered according to a protocol designed to maintain the patient within a so-called “comfort zone” that corresponds to a oesophageal pressure time between 50 and 150 $\text{cmH}_2\text{O}\cdot\text{s}\cdot\text{min}^{-1}$ [31]. Another strength of the study is that it focused on dyspnea, which is clearly a major cause of suffering for ICU patients [7]. It must be stressed that relief of dyspnea is an essential clinical objective, which,

like pain, is currently considered by some authors to be a basic human right [42, 43]. Here, the change from PSV-Baseline to either PSV-Personalization or PAV was associated with a median change > 10 mm, which is considered as the minimal clinically important difference (MCID) for D-VAS [44, 45]. In addition, dyspnea may be associated with difficult weaning and increased duration of mechanical ventilation [2]. Finally, dyspnea may be associated with unpleasant recollections following the ICU stay [9] and may contribute to the pathogenesis of post-traumatic stress disorder [11].

This study also presents a number of limitations. First, PSV was personalized according to the clinical judgment of the physician in charge of the patient. This personalization led to a conflict between the need to protect the diaphragm from over-assistance and the desire to relieve the brain from dyspnea. It is observed that even with a normal Pmus and a comfort zone in PAV+, there is a risk of over-assistance (tidal volume 9 ml/kg IBW, 70% of percentage assist). The non-randomized order of the interventions may have affected the results but the aim was to reproduce the same sequence of care as in real life; first, to personalize settings of reference mode and only this personalization fails, then change the ventilatory mode. This study evaluated only the short-term effects of changing ventilatory mode on dyspnea sensation, not the long-term effects. Subsequently, we cannot determine whether the effect of higher levels of support on dyspnea is maintained beyond this interval. Personalization based on esophageal pressure time or work of breathing may have been more accurate, but it would have required invasive measurements that cannot be transposed to daily practice. For the same reason, we did not measure the EMG activity of the diaphragm, which also requires invasive techniques. On the contrary, we focused on the EMG activity of parasternal intercostal and *Alae nasi muscles*, which can be measured noninvasively and which has been shown to be a reliable marker of respiratory drive and subsequent dyspnea [12]. Second, detection and management of patient-ventilator asynchrony was based on visual inspection of the flow and pressure trace because we wanted the study to be as less invasive as possible. Although, previous studies have suggested that, when analyzing flow and pressure signals, physicians may not be able to detect up to two-thirds of episodes of patient-ventilator asynchrony [46, 47], other studies have shown this technique to be reliable [13]. Third, it is not possible to know whether the slight discrepancy between the changes in parasternal intercostal and *Alae nasi* EMG activities is related to a technical issue with the recording of the parasternal intercostal activity (see Additional file 1: Method S1) or to a lower central respiratory drive to the parasternal intercostal muscles. Finally, we decided to include also patients with

poor communication in order to obtain a population that reflects the reality of daily practice in the ICU. Similarly, we included patients with a low dose of sedation at the time of dyspnea assessment to approximate real life. We were only able to perform a self-assessment of dyspnea in half of the subjects, which may have influenced the results.

Conclusion

In patients with clinically significant dyspnea, the PAV+ mode improves dyspnea as well as patient-ventilator asynchrony. The parallel decrease in inspiratory muscle EMG activity and the increase in breath-to-breath variability are consistent with and provide a physiological dimension to these findings. In this study, this benefit of PAV+ on dyspnea was fairly comparable to the benefit of personalization of ventilator settings in PSV. However, it should be stressed that personalization of ventilator settings in PSV must be regularly re-evaluated, which is a time-consuming procedure. This is not the case with PAV+, which constantly adapts the level of assistance delivered by the ventilator to the patient's needs. The present study paves the way to future trials investigating the benefit of PAV+ on dyspnea in larger populations.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13613-021-00958-7>.

Additional file 1. Method S1. Detailed measurement of electromyography of extradiaphragmatic inspiratory muscles. **Method S2.** Quantification of patient-ventilator asynchrony. **Method S3.** Algorithm for PAV+ adjustment. **Table S1.** Differences of dyspnea, breathing pattern and blood gases between baseline (PSV-Baseline), after optimization of ventilator settings (PSV-Personalization) and with proportional assist ventilation (PAV). **Figure S1.** Correlation between the dyspnea visual analog scale (D-VAS) and Intensive Care Respiratory Distress Observation Scale (IC-RDOS) in communicative patients (n = 18) at baseline (PSV-Baseline), after optimization of ventilator settings (PSV-Optimization) and with proportional assist ventilation (PAV). **Figure S2.** Correlation between the coefficient of variation (CV) of descriptors of the breathing pattern and dyspnea assessed by the dyspnea visual analog scale (D-VAS, left panels) and Intensive Care Respiratory Distress Observation Scale (IC-RDOS, right panels). **Figure S3.** Correlation between the pH and Intensive Care Respiratory Distress Observation Scale (IC-RDOS) in pressure support ventilation (left) and proportional assisted ventilation (right panel). **Figure S4.** Prevalence of double triggering (Panel A), prevalence of auto-triggering (Panel B) and prevalence of ineffective triggering (Panel C) at baseline (PSV-Baseline), after personalization of ventilator settings (PSV-Personalization) and with proportional assist ventilation (PAV). **Figure S5.** Correlation between the prevalence of double triggering and Intensive Care Respiratory Distress Observation Scale (IC-RDOS).

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Authors' contributions

Conception and design: CB, MD, MCN, TS, AD. Data acquisition: CB, MD, SC, MCN, TS, AD. Analysis and interpretation: CB, MD, SC, TS, AD. Drafting the manuscript: CB, MD, TS, AD. Final approval: CB, MD, SC, MCN, JM, EM, MR, TS, AD. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the *Comité de Protection des Personnes Ile de France VI* (No. 125-15). Informed consent was obtained from patients or relatives.

Consent for publication

Not applicable.

Competing interests

Dr. Alexandre Demoule reports personal fees from Medtronic, grants, personal fees and non-financial support from Philips, personal fees from Baxter, personal fees from Hamilton, personal fees and non-financial support from Fisher & Paykel, grants from the French Ministry of Health, personal fees from Getinge, grants and personal fees from Respinor, grants and non-financial support from Lungpacer, unrelated to the work submitted. Dr. Thomas Similowski reports (1) personal fees from ADEP Assistance, AstraZeneca France, Chiesi France, GSK France, Lungpacer Canada, Novartis France, Teva France; and (2) as a member of the board of a research association, unrestricted grants from Air Liquide Medical Systems, Covidien, Lungpacer, Maquet, and Philips, all unrelated to the present work. Dr. Similowski is listed as inventor on issued patents (WO2008006963A3, WO2012004534A1, WO2013164462A1) describing EEG responses to experimental and clinical dyspnea to identify and alleviate dyspnea in noncommunicative patients. Dr. Côme Bureau, Dr. Maxens Decavèle, Dr. Sébastien Campion, Marie-Cécile Nierat, Dr. Julien Mayaux, Dr. Elise Morawiec, Dr. Mathieu Raux have no conflicts of interest related to this work.

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Proportional assist ventilation relieves clinically significant dyspnea in critically ill ventilated patients

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Online Supplemental material

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Supplemental methods

Detailed measurement of electromyography of extradiaphragmatic inspiratory muscles

Collecting phasic EMG activity from the neck muscles is not straightforward. Collection by needle electrodes provides good quality signals, but the invasive nature of this collection technique precludes its use in a clinical context. The surface electrodes are in no way invasive, but the collection of the phasic activity of the neck muscles is complex given the low amplitude of the EMG signal. As a result, the signal-to-noise ratio of the phasic EMG activity of the neck muscles collected by surface electrodes is low. On the other hand, it is well shown that the averaging of the EMG signal on the surface of the scalenes makes it possible to optimize the signal-to-noise ratio (1). This method could be applied to other extradiaphragmatic inspiratory muscles such as the parasternal intercostal muscles (2) or the wings of the nose (3).

Our team has developed an alternative acquisition technique for this activity, using surface electromyography, which is non-invasive and thus achievable in clinical practice (4). Although this is an average of the electromyographic surface activity, the latter is proportional to the level of assistance that the patients need, thus testifying to the relevance of this approximation.

The primary cause of differences in impedance is the different property of the skin between individuals (5). Studies have shown that thermal noise can account for as little as 10% of the electrode-skin noise signal (5). The noise from the electrolyte-skin interface can then be estimated from measures of noise taken from recordings on the skin, and has been shown to vary between 1 and 15 μV (6).

Supplemental method 2. Algorith for PAV + ajustement

PAV+ is based on the equation of motion of the respiratory system. This equation relates the flow and volume entering the system at each point in the cycle to the total pressure required, linked to the respiratory mechanics : $(P_{tot} = P_0 + R \cdot V' + E \cdot V)$, P_{tot} : total pressure (cmH₂O) ; P_0 : start pressure (cmH₂O) ; R : resistance (cmH₂O/l. sec) ; E : elastance (cmH₂O/L) ; V' : airway flow (l/s) ; V : volume (L)). Total pressure is the sum of the airway pressure (P_{aw}), which is the assist pressure delivered by the ventilator, and the muscle pressure (P_{mus}) generated by the patient's breathing : $P_{tot} = P_{aw} + P_{mus}$. The ventilator automatically measures the elastance and resistance of the respiratory system by means of 300 millisecond teleinspiratory microocclusions. These measurements are randomised every four to ten cycles. With the elastance and resistance of the system known, the ventilator, by measuring the instantaneous flows and volumes, can calculate the value of the total pressure at each instant. The assistance delivered is then a percentage of the total pressure, and this percentage corresponds to the gain : $P_{aw} = \text{Gain} \cdot (R \cdot V' + E \cdot V) = \text{Gain} \cdot P_{tot}$. Thus, in PAV+, support is proportional to the instantaneous flow and volume and the load on the system, and therefore to the total pressure. The proportionality factor is the set gain, which is the percentage of the total pressure handled by the ventilator, the rest being handled by the patient's breathing muscles. The airway pressure delivered by the ventilator in PAV+ is therefore directly proportional to the instantaneous muscle pressure of the patient. The only proportionality factor in the equation is the set gain : $P_{aw} = (\text{Gain}/[1 - \text{Gain}]) \cdot P_{mus}$.

As PAV+ offers the possibility of monitoring a reproducible respiratory effort index, we used the simple gain adjustment modality to conduct weaning in PAV+ (7).

The gain adjustment protocol during PAV+ ventilation was that of Carteaux et al. and was designed to keep the patient within a reasonable target range of respiratory effort, which we defined as a respiratory muscle pressure-time product (PTP_{mus}) between 50 and 150 cm H₂O-s/min. As PTP_{mus} cannot be calculated at the bedside, we used its main component as a

surrogate: the peak muscle pressure of the respiratory muscles ($P_{mus,Peak}$). This pressure is the maximum swing of the inspiratory muscles during inspiration, estimated using the following equation: $(Peak\ airway\ pressure - Positive\ end-expiratory\ pressure\ (PEEP) \times ((100 - Gain) / Gain)$. A grid built from this equation was available at the bedside (Carteaux), allowing the rapid estimate of the $P_{mus,Peak}$. From the values of the gain, the PEEP, and the $P_{aw,Peak}$, which all are available on the screen of the ventilator, the $P_{mus,Peak}$ can be immediately estimated.

The parameters at PAV initiation were set to a Gain of 50% and an inspiratory trigger of 2 l/min. The adjustment algorithm is defined as a function of the $P_{mus, peak}$. If $P_{mus, peak}$ is less than 5 cmH₂O, the gain is reduced in 10% steps until the pressure reaches the target range. If the pressure is higher than 10 cmH₂O the gain is increased by 10% steps. If $P_{mus,peak}$ is between 5 and 10 cmH₂O no change is made unless the V_{te} exceeds 10 ml/kg of PBW without any obvious cause of hyperventilation justifying a decrease in gain by 10% steps or if the V_{te} falls below 5 ml/kg despite an optimization of FiO_2 and PEP.

Supplemental method 3. Quantification of patient-ventilator asynchrony

The following three main patterns of patient-ventilator asynchrony were quantified: 1) ineffective triggering, 2) auto triggering, 3) double triggering. Premature cycling and late cycling could not be quantified because the analysis could not be done visually.

These patterns of asynchrony were quantified according to a detection methods based on flow and airway pressure signals only by visual inspection of the recordings.

The three main patterns of asynchrony were quantified off-line by the same investigators (C.B.), intensivists trained in detection of patient-ventilator asynchronies, who analyzed all the breaths. The investigator categorized each analyzed breath as "asynchrony" or "no asynchrony" according to the definition.

The asynchrony index (AI) was computed as the number of asynchronous breaths divided by the total number of breaths (both requested and delivered) multiplied by 100.

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Table S1. Differences of dyspnea, breathing pattern and blood gases between baseline (PSV-Baseline), after optimization of ventilator settings (PSV-Personalization) and with proportional assist ventilation (PAV)

	Change between PSV-Personalization and PSV-baseline	Change between PAV and PSV-Personalization	Change between PAV and PSV-baseline	<i>p</i>
<i>Dyspnea</i>				
D-VAS, <i>mm</i>	-13 (-26--8)*	-2 (-11-0)	-17 (-30--10)*	0.001
IC-RDOS	-0.07 (-2.00-0.01)	-0.02 (-0.15-0.5)	-1.85 (-2.09-- 0.01)*	0.002
<i>Breathing pattern</i>				
RR, <i>min⁻¹</i>	-2 (-5-0)*	-3 (-5-0)*	-4 (-9--2)*	<0.0001
V _T , <i>ml/kg IBW</i>	0.8 (0.2-1.9)*	0.6 (-0.5-2.2)	1.7 (0.5-2.6)*	<0.0001
T _i , <i>sec</i>	0.08 (-0.01-0.18)	0.17 (0.05-0.25)*	0.22 (0.13-- 0.34)*	<0.0001
V _T / T _i , <i>L/s⁻¹</i>	0.51 (0.10-1.35)*	-0.95 (-2.29--0.29)*	-0.19 (-0.49-- 0.04)	<0.0001
P _{max} , <i>cmH₂O</i>	7 (6-9)*	4 (0-7)	11 (7-14)*	<0.0001
EtCO ₂ , <i>mmHg</i>	-1 (-2-0)	0 (-1-2)	0 (-1-0)	0.033
<i>Breath-by-breath variability</i>				
CV RR, %	1 (-3-7)	4 (-2-11)*	6 (1-16)*	0.001
CV V _T , %	0 (-5-3)	10 (3-18)*	10 (-1-25)*	< 0.001
CV T _i , %	3 (-3-15)	-13 (-23-1)*	-4 (-22-6)	0.023
CV V _T / T _i , %	1 (-7-11)	0 (-14-27)	2 (-9-32)	0.632
CV P _{max} , %	1 (-1-4)	9 (5-17)*	10 (6-17)*	< 0.001
<i>Blood gases</i>				
pH	0.02 (0.01-0.03)*	0.01 (-0.01-0.02)	0.01 (0.00-- 0.03)*	0.012
PaO ₂ , <i>mmHg</i>	2 (3-9)	5 (-12-14)	6 (-1-15)*	0.016
PaCO ₂ , <i>mmHg</i>	-2 (-2-1) *	1 (-2-3)	-1 (-3-1)	0.001
SaO ₂ , %	0 (0-1)	1 (0-3)	2 (0-2)	0.038
HCO ₃ ⁻ , <i>mmol/L</i>	0.2 (-0.2-0.3)	-0.1 (-0.3-0.3)	0 (-0.2-0.2)	0.503

D-VAS, Dyspnea visual analog scale, IC-RDOS, Intensive Care Respiratory Distress Observation Scale, RR, respiratory rate; Ti, inspiratory time; VT tidal volume; IBW, ideal body weight; EtCO₂, CO₂ expired fraction; CV, coefficient of variation; Pmax, peak airway pressure
Data are expressed as median (interquartile range); * p <0.05

Figure S1. Correlation between the dyspnea visual analog scale (D-VAS) and Intensive Care Respiratory Distress Observation Scale (IC-RDOS) in communicative patients (n = 18) at baseline (PSV-Baseline), after optimization of ventilator settings (PSV-Optimization) and with proportional assist ventilation (PAV)

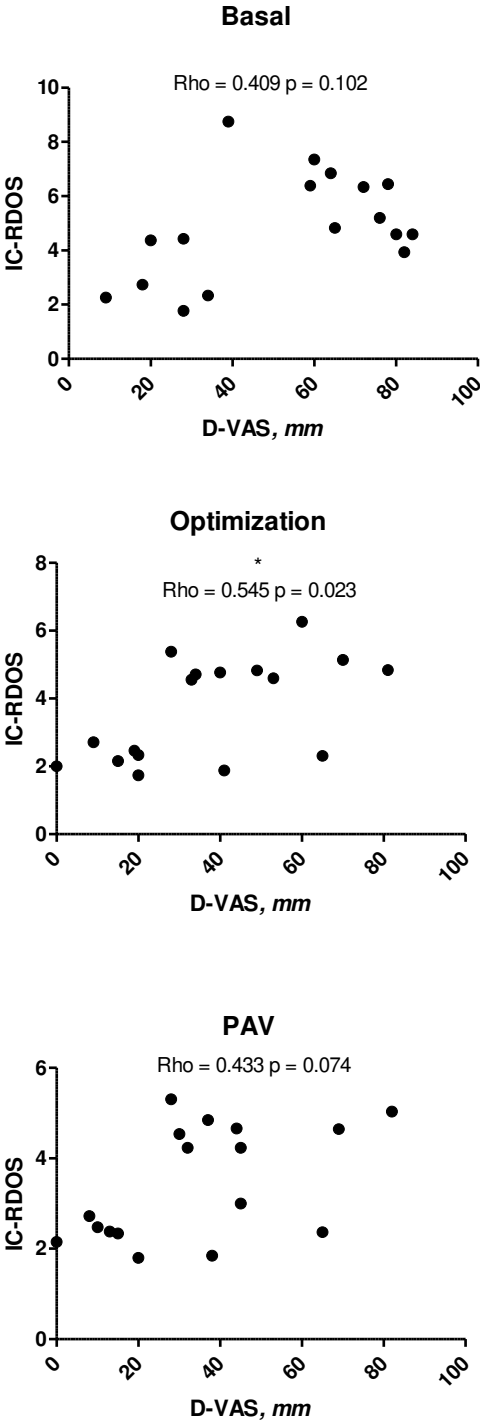
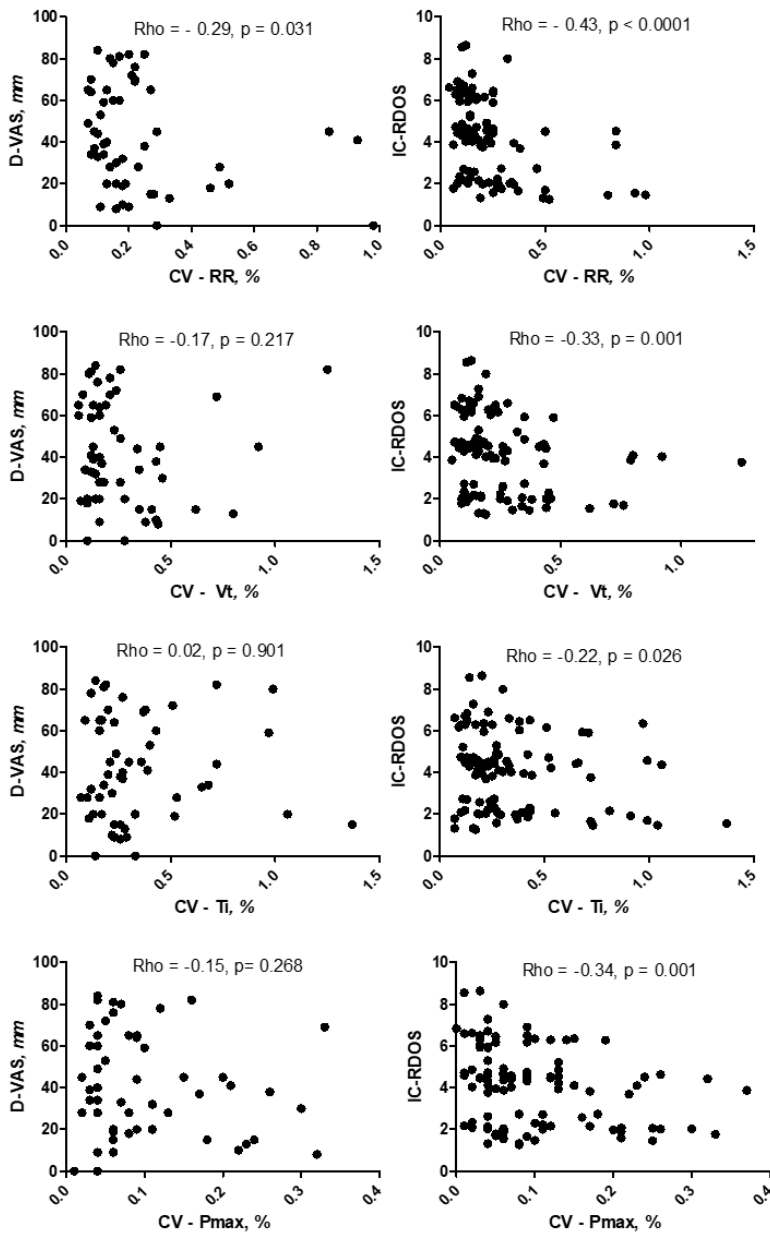


Figure S2. Correlation between the coefficient of variation (CV) of descriptors of the breathing pattern and dyspnea assessed by the dyspnea visual analog scale (D-VAS, left panels) and Intensive Care Respiratory Distress Observation Scale (IC-RDOS, right panels)



RR: respiratory rate, Pmax: maximal inspiratory pressure, Ti: inspiratory time, Vt: tidal volume

Figure S3. Correlation between the pH and Intensive Care Respiratory Distress Observation Scale (IC-RDOS) in pressure support ventilation (A) and proportional assisted ventilation (B) and correlation between the bicarbonatemia and IC-RDOS in pressure support ventilation (C) and proportional assisted ventilation (D)

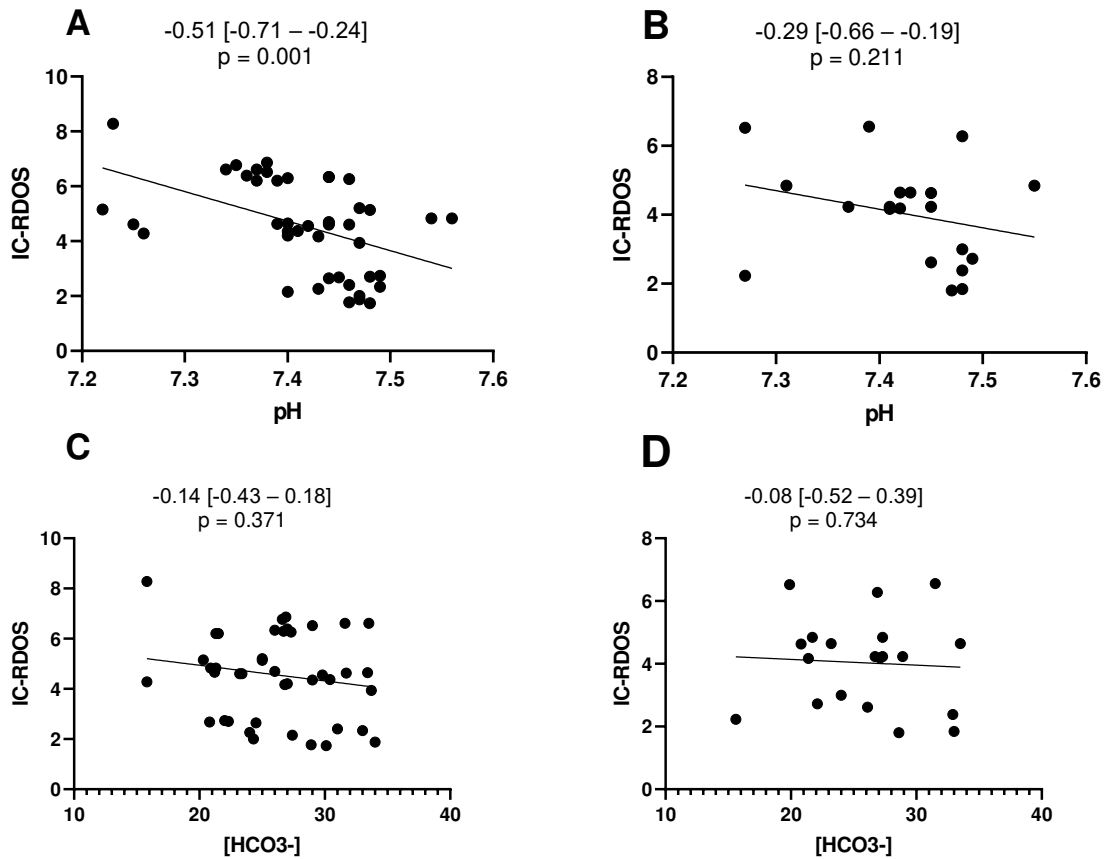
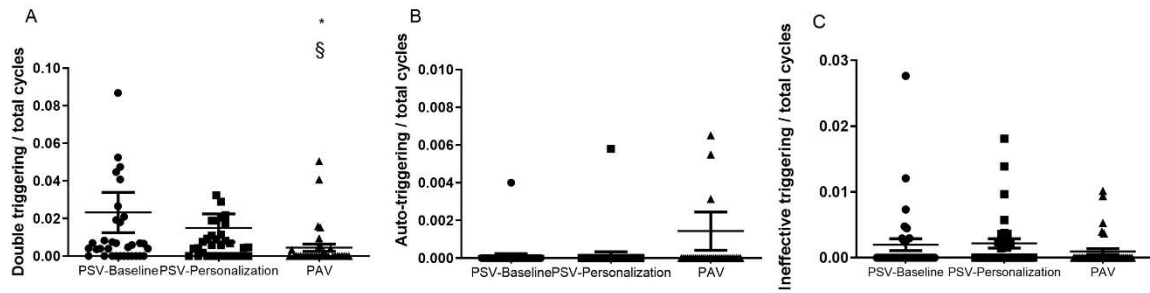


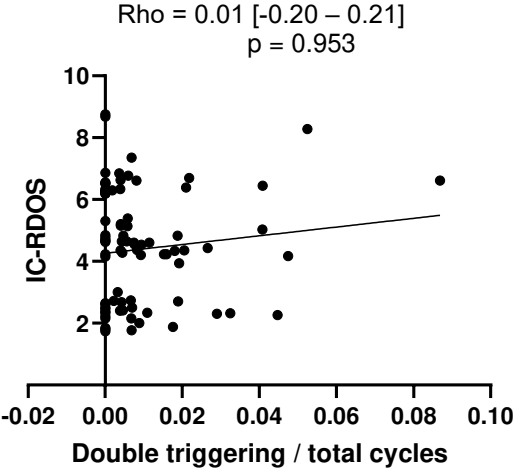
Figure S4. Prevalence of double triggering (Panel A), prevalence of auto-triggering (Panel B) and prevalence of ineffective triggering (Panel C) at baseline (PSV-Baseline), after personalization of ventilator settings (PSV-Personalization) and with proportional assist ventilation (PAV)



The horizontal solid line indicates median value.

* p <0.05 compared to PSV-Baseline, § p <0.05 compared to PSV- Personalization

Figure S5. Correlation between the prevalence of double triggering and Intensive Care Respiratory Distress Observation Scale (IC-RDOS)





Sensory interventions to relieve dyspnea in critically ill mechanically ventilated patients

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Abstract:	<p>Rationale. In critically ill patients receiving mechanical ventilation (MV), dyspnea is frequent, severe, and associated with an increased risk of neuropsychological sequelae. We evaluated the efficacy of sensory interventions targeting the brain rather than the respiratory system to relieve dyspnea in MV patients.</p> <p>Methods. Patients receiving MV for ≥ 48 hours and reporting dyspnea (unidimensional dyspnea visual analogue scale [Dyspnea-VAS]) first underwent increased pressure support, and were then, in random order, auditory stimulation (relaxing music vs. pink noise) and air flux stimulation (facial vs. lower limb). Treatment responses were assessed using Dyspnea-VAS, the Multidimensional Dyspnea Profile, and measures of the neural drive to breathe (P0.1; electromyogram of inspiratory muscles).</p> <p>Main Results. We included 46 patients (tracheotomy or intubation $n=37$, non-invasive ventilation $n=9$). Increasing pressure support decreased Dyspnea-VAS by median 40 mm ($p<0.001$). Exposure to music decreased Dyspnea-VAS compared exposure to pink noise by 40 mm ($p<0.001$). Exposure to facial air flux decreased Dyspnea-VAS compared to limb air flux by 30 mm ($p<0.001$). Increasing pressure support, but not music exposure and facial air flux, reduced P0.1 (by 3.3 cmH₂O; $p<0.001$).</p> <p>Conclusions. In MV patients, sensory interventions can modulate the processing of respiratory signals by the brain irrespective of the intensity of the neural drive to breathe. It should therefore be possible to alleviate dyspnea without resorting to pharmacological interventions or having to infringe the constraints of MV lung protection strategies by increasing ventilatory support.</p>
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Sensory interventions to relieve dyspnea in critically ill mechanically ventilated patients

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CB and AD directly accessed and verified the underlying data reported in the manuscript.

All authors should confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

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"Take home" message: In mechanical ventilated patients, sensory interventions can modulate the processing of respiratory signals by the brain and alleviate dyspnea without pharmacological interventions or having to infringe the constraints of lung protection strategies.

Data sharing statement

All data collected for the study, including individual participant data will be made available upon request to the sponsor (participant data with study participation code, study protocol, informed consent form).

Trial registration: NCT04815317.

ABSTRACT (232 words [max 250 words])

Rationale. In critically ill patients receiving mechanical ventilation (MV), dyspnea is frequent, severe, and associated with an increased risk of neuropsychological sequelae. We evaluated the efficacy of sensory interventions targeting the brain rather than the respiratory system to relieve dyspnea in MV patients.

Methods. Patients receiving MV for ≥ 48 hours and reporting dyspnea (unidimensional dyspnea visual analogue scale [Dyspnea-VAS]) first underwent increased pressure support, and were then, in random order, auditory stimulation (relaxing music vs. pink noise) and air flux stimulation (facial vs. lower limb). Treatment responses were assessed using Dyspnea-VAS, the Multidimensional Dyspnea Profile, and measures of the neural drive to breathe (P0.1; electromyogram of inspiratory muscles).

Main Results. We included 46 patients (tracheotomy or intubation n=37, non-invasive ventilation n=9). Increasing pressure support decreased Dyspnea-VAS by median 40 mm ($p < 0.001$). Exposure to music decreased Dyspnea-VAS compared exposure to pink noise by 40 mm ($p < 0.001$). Exposure to facial air flux decreased Dyspnea-VAS compared to limb air flux by 30 mm ($p < 0.001$). Increasing pressure support, but not music exposure and facial air flux, reduced P0.1 (by 3.3 cmH₂O; $p < 0.001$).

Conclusions. In MV patients, sensory interventions can modulate the processing of respiratory signals by the brain irrespective of the intensity of the neural drive to breathe. It should therefore be possible to alleviate dyspnea without resorting to pharmacological interventions or having to infringe the constraints of MV lung protection strategies by increasing ventilatory support.

INTRODUCTION

Dyspnea, a symptom conveying an upsetting or distressing awareness of breathing, is associated with deeply traumatic experiences [1]. It is reported by 35% to 50% of all critically ill patients receiving mechanical ventilation (MV) [2-4] who describe it as one of the worst aspects of MV [5], and dyspnea under MV is associated with post-traumatic stress disorder [3]. Relieving dyspnea should therefore be a primary clinical concern, as is already the case for relieving pain [6]. As with pain, the active identification and the effective management of dyspnea are in the realm of human rights [7, 8].

Dyspnea is associated with respiratory-related brain activation that is considered to stem from a mismatch between the outflowing neural drive to breathe and the corresponding afferent return (corollary discharge theory) [1, 9], with strong associations between the intensity of dyspnea and the intensity of the neural drive to breathe. In the event of a load-capacity imbalance of the respiratory muscle [10], which is frequent in Intensive Care Unit (ICU) patients, increasing ventilatory support is particularly effective for reducing the neural drive to breathe and at relieving dyspnea [2, 10, 11]. However, the guidelines for lung protective ventilation may limit this option [12] and lead to a difficult clinical quandary. Therapeutically, this involves a paradigm shift from targeting the respiratory system to targeting the brain [13]. In this context, opioids can relieve dyspnea [14], but the associated risk-benefit balance in MV patients is not known [15]. Outside the ICU, when abnormalities that trigger dyspnea cannot be corrected, alternative approaches have been described [16]. Directing a flux of air to the face has been shown to alleviate dyspnea [17, 18], probably through the brain misinterpreting the corresponding trigeminal stimulation as an increased respiratory-related afferent traffic (the "fool the brain" concept [19]). Music can also alleviate dyspnea [20], perhaps as a consequence of attentional distraction or of an anxiety-reducing effect (the "appease the mind" concept [21]).

Dyspnea is a multidimensional experience with sensory and affective dimensions in reciprocal interaction, and acting on either or both of these dimensions can provide dyspnea relief.

We hypothesised that brain-targeted interventions (trigeminal stimulation and auditory stimulation) would reduce the intensity of dyspnea in critically ill MV patients and that this would occur independently of concomitant reductions in the neural drive to breathe. We also hypothesised that such interventions would be effective on the affective dimension of dyspnea.

PATIENTS AND METHODS

This single-centre prospective study (NCT04815317) was performed in a 22-bed medical ICU and a 12-bed weaning centre at La Pitié-Salpêtrière University Hospital, Paris, France between November 2019 and August 2021. The study protocol and one amendment were approved by the *Comité de Protection des Personnes Ouest 5 Rennes* (No. 19/073-2) and written informed consent was obtained from each patient.

Patients

Patients who met the following criteria were eligible: 1) invasive MV (endotracheal probe or tracheostomy) ≥ 48 hours or non-invasive ventilation (NIV) ≥ 24 hours, sequential or continuous; 2) dyspnea under MV at screening ≥ 40 mm on a dyspnea Visual Analogue Scale (Dyspnea-VAS) from 0 ("no respiratory discomfort") to 100 mm ("worst imaginable respiratory discomfort"); 3) absence of delirium as assessed by the CAM-ICU, 4) communicative patient, with a Richmond Agitation-Sedation Scale (RASS) between -1 and +1, no severe cognitive impairment, no severe mental illness, no severe hearing loss, adequate command of French, and ability to execute the five following orders: open and close eyes, look at examiner, nod, open mouth and stick out tongue, and raise eyebrows at examiner's count of five. Non-inclusion criteria were: 1) patients on extracorporeal circulation; 2) immediate postoperative patients of any surgery; 3) age < 18 years or in legal guardianship; 4) known pregnancy; 5) refusal to participate.

Measurements

Anthropometric data, medical history, and ongoing treatments were collected at inclusion.

Assessment of dyspnea

Dyspnea was assessed using a unidimensional 100 mm VAS (0: absence of any breathing discomfort; 100: maximal imaginable breathing discomfort) and also assessed using the French version of the Multidimensional Dyspnea Profile (MDP) questionnaire [22], which comprises

an unpleasantness score (A1), a sensory score (SQ) and an emotional score (A2). A detailed description of the MDP questionnaire, how questions were presented to patients, and how the three MDP subscores were calculated is provided in [Supplemental Methods 1](#). Briefly, The A1 score assessed the unpleasantness of breathing using an ordinal scale ranging from 0 (“neither pleasant nor annoying”) to 10 (“unbearable”). The SQ score assessed five sensory descriptors (physical breathing effort, air hunger, tightness, mental breathing effort, and hyperpnoea) with an ordinal scale from 0 to 10, (0 corresponding to the absence of the sensation and 10 corresponding to the highest imaginable intensity). The A2 score assessed five emotions (depressed, anxious, angry, frustrated and afraid) with an ordinal scale from 0 to 10 (0 corresponding to the absence of the emotion and 10 corresponding to the highest imaginable intensity). The maximum score for A1 was 10 and was 50 for SQ and A2. The sum (A1+SQ) defines the immediate perception domain and A2 the emotional domain; SQ defines the sensory dimension and (A1+A2) defines the affective dimension of dyspnea.

Verbatim report

Patients were asked to express their feelings after receiving the two brain-targeted interventions (Air-Face and Relaxing-Music) which were reported verbatim ([Supplemental Methods 2](#)).

Airway pressure and flow

Airway flow was measured using a pneumotachograph (Hans Rudolph, Kansas City, USA) inserted between the Y-piece and the endotracheal tube before being connected to a differential pressure transducer (Validyne, Northridge, USA). Airway pressure was measured at the Y-piece by a differential pressure transducer (Validyne, Northridge, USA).

*Electromyography (EMG) of inspiratory muscles (parasternal intercostal muscle and *Alea nasi*)*

The EMG signal of the extra-diaphragmatic inspiratory muscles is a surrogate for central respiratory drive [23]. The EMG signal of the *Alea nasi* and parasternal intercostal muscles was

collected by self-adhesive surface electrodes similar to those commonly used for electrocardiogram recording in critically ill patients, with an interval of 2 cm between the two electrodes ([Supplemental Methods 3](#)).

Airway occlusion pressure (P0.1) measurement

P0.1 is defined as the negative pressure measured at the airway opening 100 ms after the initiation of an inspiratory effort performed against a closed respiratory circuit [24]. It is a surrogate for central respiratory drive [25]. This measure is automated in modern ICU ventilators [26]. P0.1 could not be collected in patients receiving non-invasive ventilation.

Arterial blood gases

If an arterial catheter was present, blood gases were collected at the end of each experimental condition.

Sensory and emotional modulation of dyspnea

Patients were exposed to three different interventions intended to modulate dyspnea; each intervention was compared to a control situation.

Increase in pressure support level

The intervention was termed “PS-Increase” and consisted of increasing the pressure support level by 5 cmH₂O. The control condition, termed “Baseline-PS”, was the baseline pressure support level on inclusion. “PS-Increase” was performed in Patients #15 to #46 only, after approval of a protocol amendment.

Flux of air

The intervention was termed “Air-Face” and consisted of blowing air in the patient’s face using a bladeless fan (Dyson AM01, Malmesbury, UK) placed at a comfortable distance. The control condition, termed “Air-Leg” consisted of blowing air over one of the patient’s legs [18].

Auditory stimulus

The intervention was termed “Relaxing-Music” and consisted of listening with headphones (on-ear headset, wired, retractable NUBWO N16, Docooler, USA) to three successive, relaxing musical pieces from a list of music programs from the International Center for Music Therapy (Noisy le Grand, France; douceur, relaxation, bien-être, Eric Aron, Eric Breton, Charles Webb, label Art Com). The control condition, termed “Pink-Noise” (Pink Noise, Acerting Art, White Noise Sounds Compilation, Spotify, USA), consisted of listening to pink noise with the same headphones, a random signal for which the power spectral density decreased by 3 dB per octave, which is close to the ear sensitivity [27].

Study design

Figure 1 shows the study design. Six conditions were studied, and each lasted 10 minutes. The first condition was “Baseline-PS”, followed by “PS-Increase”. Next, the order in which the four remaining conditions were applied was randomised. First, the initial use of flux of air or auditory stimulus was randomised. Second, the initial use of control or stimulus was randomised. Conditions were separated by a 10-minute washout period.

Mechanical ventilation was delivered with a Carescape R860 ventilator (GE Healthcare, USA) or a V500 ventilator (Dräger, Lubeck, Germany). Ventilator settings remained constant across conditions, excepted for pressure support level in the PS-Increase condition.

Data analysis

Breathing pattern

Breathing pattern variables were determined on a breath-by-breath basis for each of the six conditions (Labchart 7.3® software, ADInstruments, Dunedin, New Zealand). These included instantaneous respiratory rate (RR), tidal volume (VT), inspiratory time (Ti), and maximal inspiratory pressure (Pmax).

Electromyogram (EMG) of extra-diaphragmatic inspiratory muscles

Inspiratory muscle EMG activity, used to estimate respiratory drive, was processed using the Labchart Peak Analysis module MLS380/8 (ADInstruments, Dunedin, New Zealand). EMGmax and EMGauc were expressed as a proportion of the activity measured under the control condition ([Supplemental Methods 3](#)).

Statistical analysis

Statistical analysis was performed using Prism 8.0 software (GraphPad Software, San Diego, CA, USA). Continuous variables were described by their median and interquartile interval. Categorical variables were expressed in absolute value and percentage. All analyses were performed with a type I error of 5%. Intervention and control conditions were compared using the Wilcoxon signed-rank test for continuous variables and using the McNemar test for categorical variables. Comparison of continuous variables between the three control conditions and of the difference between the intervention and control conditions during pressure support increase, flux of air, and auditory stimulus were done using the Friedmann test, followed, when positive, by a *post hoc* comparison using the Dunn test. Correlations between variables were evaluated using the Spearman rank correlation coefficient.

For the sample size calculation, according to previous reports, we expected that interventions would reduce Dyspnea-VAS by 25% compared to their respective control [18]. Since median Dyspnea-VAS is 50 mm in dyspnoeic MV patients, this 25% reduction corresponded to a reduction of dyspnea by 12.5 mm, which is more than the minimally clinical important difference (10 mm) for Dyspnea-VAS in other clinical contexts [28]. With an alpha risk of 5% and a power of 90%, a sample size of 45 patients was required.

Role of the funding source

Financial support was provided supported by Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France (for Dr Côme Bureau), and a Pilot Study Grant was provided by Fondation du Souffle, Paris, France.

RESULTS

Overall, 1367 patients were admitted and required MV, 1069 invasive MV and 298 NIV. Of these, 1321 did not meet the inclusion criteria or met at least one of the non-inclusion criteria: 260 received invasive MV <48 h or NIV <24 h, 458 had Dyspnea-VAS <40 mm, 34 had delirium according to CAM-ICU, 152 were non communicative, three were <18 years old, 147 declined to participate, and 267 were excluded for a technical reason (eg, equipment failure, weekend). The detailed patient disposition is presented in [Figure S1](#).

Forty-six patients were included, 29 (59%) in the ICU and 19 (41%) in the weaning unit ([Table 1](#)). Eighteen patients (39%) were connected to the ventilator using an endotracheal tube, 19 (41%) were tracheotomised and 9 (20%) received NIV with a face mask. Of these 46 patients, 32 patients had a change in pressure support. Air-Face and Relaxing-Music were studied in all patients except for 4 patients who found the duration of the experiment too long and who wished to stop before completing all the conditions.

Breathing pattern and blood gases

Breathing pattern and blood gases across the six experimental conditions are reported in [Table 2](#). Compared to its control, PS-Increase was associated with a lower respiratory rate ($p=0.009$), while no difference was shown for Air-Face and Relaxing-Music versus the controls. Compared to its control, PS-Increase was associated with higher V_T and longer T_i , while Air-Face and Relaxing-Music were not associated with differences in these variables. Compared to their respective control conditions, each the three interventions was associated with a lower heart rate.

Dyspnea

Unidimensional Dyspnea-VAS and A1 (respiratory discomfort), SQ (sensory dimension) and A2 (emotional response) components of the MDP questionnaire across the six experimental conditions are reported in [Figure 2](#) (see also [Table S1](#) and [Table S2](#) for detailed values of the

MDP questionnaire). Dyspnea-VAS was not different between the three control conditions (PS-Increase, Air-Leg, Pink-Noise, $p=0.116$). Compared to their respective control conditions, the three interventions decreased Dyspnea-VAS, A1, QS, Immediate perception domain (A1+QS), and Affective dimension (A1+A2). Compared to their respective control conditions, Air-Face and Relaxing-Music decreased A2 ($p<0.0001$) whereas PS-Increase did not decrease A2 ($p = 0.174$).

When the difference between an intervention and its control condition was considered, the decrease in Dyspnea-VAS was higher with PS-Increase (-40 [-50 – -40] mm) and Relaxing-Music (-40 [-50 – -30] mm) than with Air-Face (-30 [-40 – -20] mm, $p = 0.001$). For the MDP questionnaire, the decrease in the A1 affective score was higher for Relaxing-Music (-5 [-7 – -4]) than for PS-Increase (-2 [-3 – -1]) and was higher for Air-Face (-7 [-4 – -11]) than for the two other conditions ($p<0.001$). The decrease in the QS sensory score was higher for Air-Face (-11 [-14 – -7]) than for PS-Increase (-8 [-12 – -6]) and was higher for Relaxing-Music (-13 [-19 – -9]) than for the two other conditions ($p<0.001$). The same pattern was observed with the A2 emotional score (-7 [-5 – -3] for Relaxing-Music vs. -4 [-8 – -2] for Air-Face vs. 0 [-1 – 0] for PS-Increase, $p<0.001$).

P0.1 and extradiaphragmatic inspiratory muscle EMG activity

P0.1 and EMG activity of the *Alea nasi* and parasternal intercostal muscles across the six conditions are reported in [Figure 3](#) (see also [Table S2](#)). When compared to Baseline-PS, the EMG activity of the *Alea nasi* and parasternal muscles was lower in the PS-Increase condition ($p<0.0001$), while Air-Face and Relaxing-Music were not associated with changes in EMG activity of the *Alea nasi* and parasternal muscles compared to their respective control conditions. The three interventions were associated with a decrease in P0.1 compared to their respective control conditions. When compared to their respective control conditions, the

decrease in P0.1 was higher with PS-Increase (-3.3 [-3.7 – -2.3] cmH₂O) than with Air-Face (-0.3 [-0.9 – 0] cmH₂O) and Relaxing-Music (-0.3 [-1.0 – 0] cmH₂O, p<0.001).

Dyspnea and P0.1 measurement correlations

Correlations between P0.1 and Dyspnea-VAS across the six conditions are reported in [Figure 4](#). Significant correlations between P0.1 and Dyspnea-VAS were present in Baseline-PS (p=0.004), PS-Increase (p=0.009), Air-Leg (p=0.003) and Pink-Noise (p=0.009). In contrast, no significant correlation was observed during Air-Face (p=0.351) and during Relaxing-Music (p=0.414). A similar finding was observed with the correlation between P0.1 and the A1 component of the MDP questionnaire ([Figure S2](#)).

The correlations between difference between intervention and control condition for P0.1 and difference between intervention and control condition for Dyspnea-VAS during pressure support increase, flux of air and auditory stimulus are reported in [Figure S3](#). A significant correlation between difference of Dyspnea-VAS and difference of P0.1 was present for PS-Increase (p=0.015) but not for flux of air (p=0.340) nor for auditory stimulus (p=0.680).

Subpopulations of tracheotomised, intubated and NIV patients

Dyspnea, EMG activity of the extra-diaphragmatic inspiratory muscles and P0.1 across the six conditions are reported for the subpopulation of tracheotomised patients ([Table S3](#)), intubated patients ([Table S4](#)), and those receiving NIV ([Table S5](#)).

Verbatim report

The verbatim reports of the 41 patients reporting their experience after Relaxing-Music and Air-Face are included in [Figure S4](#) and [Figure S5](#).

DISCUSSION

This study showed that two brain-targeted sensory interventions (air flux stimulation to the face and relaxing music) provided clinically relevant relief from dyspnea in critically ill MV patients. This relief concerned both the sensory and affective dimensions of dyspnea. Furthermore, it occurred independently of any change in MV settings, without V_T increases, and independently of the neural drive to breathe. In contrast, increased pressure support, a respiratory-targeted intervention associated with an increased V_T and decreased drive to breathe, was only effective in the sensory dimension.

Over the past decade, the appropriate management of dyspnea has been shown to be a prominent concern in ICU patients [6, 8]. Dyspnea is frequent and severe in this population and has short- and long-term deleterious consequences [2, 3]. One of the most recent and significant developments in the field of dyspnea is the recognition of its multidimensional nature [1, 22, 29], with both sensory and affective dimensions that stem from cognitive and affective processes[1] and are dominated by anxiety and fear. Clinical relief can derive from therapeutic interference in either the sensory or affective dimensions, or both [30].

In our patients, PS-Increase alleviated the sensory component of dyspnea, most likely in line with an improved load-capacity balance of the respiratory muscle and reduced respiratory drive [10, 31, 32], evidenced by decreased P0.1 and inspiratory muscle EMGs. According to the corollary discharge theory (see Introduction), it can be postulated that PS-Increase rebalanced the respiratory output-input equilibrium. Of note, PS-Increase did not interfere with the affective component of dyspnea. As expected, the efficacy of PS-Increase was associated with an increased V_T , which could be deleterious in patients with injured lungs. Air-Face and Relaxing-Music also decreased the sensory dimension of dyspnea (including its air hunger component; see [Table S1](#)). In stark contrast with PS-Increase, this effect was obtained without changes in V_T and independently of any change in respiratory drive. This was well illustrated

by the loss of the dyspnea-drive correlation seen within the other conditions (Figure 4). The relief of dyspnea (and air hunger) without modification of the respiratory output-input equilibrium suggests that the corollary discharge mechanism is not the only one involved in the pathogenesis of dyspnea. In this regard, it is important to emphasize that, in contrast with PS-Increase, Air-Face, and Relaxing-Music were effective at reducing the affective component of dyspnea. Of note, the three interventions (PS-Increase, Relaxing-Music, and Air-Face) were all associated with a decrease in heart rate, suggesting a similar impact of each one on the neurovegetative manifestations associated with dyspnea [2, 33].

Previous studies have evaluated the effect of sensory interventions on dyspnea in healthy volunteers and patients. The administration of a fresh flux of air to the face of healthy volunteers reduced the intensity of dyspnea in a model of resistive loading [17]. This effect was not shown when the air was applied to the calf [17]. In palliative care patients, face-directed fan air therapy decreased dyspnea intensity by 30% [18]. In patients with chronic obstructive pulmonary disease, listening to music during a 6-minute walk test decreased the intensity of dyspnea [20, 34], primarily through its affective component [34]. We found very little data on fan therapy and music in MV patients. In one study in patients requiring non-invasive ventilation for acute respiratory failure, a musical intervention did not relieve dyspnea, but did affect neurovegetative outcomes [35]. In this study, however, dyspnea was not assessed in a multidimensional manner, which could have obscured a dissociated sensory-affective [36].

Our study appears to be the first dyspnea interventional study of this size using a controlled design in MV patients. Its main strength is the demonstration of the efficacy of two simple and non-invasive brain-targeted non-pharmacological interventions to alleviate dyspnea. These interventions appear at least as effective as "traditional" approaches such as pressure support augmentation. They have the primary advantage of providing dyspnea relief without the need to increase VT and the corresponding risk of volume-induced lung injury [37]. Of note, our

observations are also of interest in the context of the reluctance to use opioids in MV patients because of the risk of ventilatory depression [38], even though opioids are effective and safe for the relief of dyspnea [10, 11]. Our study included some limitations. First, dyspnea was assessed without blinding of either the patient or the assessor. However, such blinding would have been technically challenging. Second, the study was necessarily conducted in fully communicative patients, because dyspnea is self-reported. Non-communicative patients, patients with delirium, and those who did not understand French were not included, which constitutes a selection bias. Third, our study was not designed to evaluate the long-term benefits of dyspnea relief, and data collection was limited to short-term effects only: the study did not provide data on the durability of the effects over time, and waning through habituation cannot be excluded. Finally, the study did not provide a mechanistic explanation of the observed effects, as could have been provided by electroencephalography, for example [39].

In conclusion, our observations demonstrate that it is possible to address dyspnea under MV without increasing the level of ventilatory support, namely without increasing lung volume. ‘Dyspnea under MV is, therefore, not a mandatory price to pay in the management of respiratory distress [40]. The study provides the scientific rationale for clinical trials evaluating robust and long-term outcomes of brain-targeted interventions for the relief of dyspnea.

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TABLES

Table 1. Characteristics of the study population (n = 46)

<i>Demographic characteristics</i>	
Gender, <i>male, n (%)</i>	34 (74)
Age, <i>years</i>	63 (54–73)
Body Mass Index, <i>kg.m⁻²</i>	25 (21–28)
<i>Comorbidities</i>	
Chronic respiratory disease, <i>n (%)</i>	12 (26)
Chronic heart failure, <i>n (%)</i>	6 (13)
<i>Reason for intubation</i>	
SARS-CoV-2 pneumonia, <i>n (%)</i>	12 (26)
Non SARS-CoV-2 pneumonia, <i>n (%)</i>	11 (24)
Coma, <i>n (%)</i>	6 (13)
Acute cardiogenic pulmonary oedema, <i>n (%)</i>	4 (8)
Acute-on-chronic respiratory failure, <i>n (%)</i>	4 (8)
Other, <i>n (%)</i>	9 (21)
<i>Duration of mechanical ventilation prior to inclusion</i>	
In intubated patients, <i>days</i>	9 (4–17)
In tracheotomised patients, <i>days</i>	57 (38–99)
In non-invasive ventilation patients, <i>days</i>	12 (2–18)
<i>Severity scores</i>	
SAPS 2 at intensive care unit admission	43 (29–53)
SOFA at inclusion	4 (3–6)
<i>At inclusion</i>	
Sedation, <i>n (%)</i>	10 (22)
Richmond Agitation and Sedation Scale	0 (0–0)
Pain visual analogic scale at the inclusion, <i>mm</i>	0 (0–0)
<i>Ventilator settings at inclusion</i>	
Inspired oxygen fraction, <i>%</i>	35 (30–40)
Positive end-expiratory pressure, <i>cmH₂O</i>	6 (5–7)
Pressure support level, <i>cmH₂O</i>	12 (10–14)
Inspiratory trigger, <i>L/min</i>	1 (1–1)
Cycling off, <i>%</i>	25 (25–30)

SAPS, Simplified Acute Physiology Score; SOFA, Sepsis-related Organ Failure Assessment.
Data are expressed as median (interquartile range) and number (%)

Table 2. Breathing pattern, hemodynamic pattern, and blood gases during pressure support, flux of air, and auditory stimulus

	Baseline pressure support	Pressure support increase	p	Air Leg	Air Face	p	Pink noise	Relaxing music	p
<i>Breathing pattern</i>									
Respiratory rate, min^{-1}	24 (20–31)	23 (18–27)	0.009	26 (19–32)	24 (20–31)	0.069	25 (20–29)	25 (21–29)	0.643
Tidal volume, <i>ml</i>	470 (325–582)	686 (505–950)	<0.0001	468 (335–586)	474 (337–599)	0.642	470 (317–579)	498 (308–584)	0.152
Tidal volume, <i>ml/kg IBW</i>	6.7 (5.8–8.3)	8.7 (7.2–11.1)	<0.0001	6.8 (5.5–8.4)	6.5 (5.6–7.8)	0.268	6.7 (5.9–8.1)	6.5 (5.8–9.1)	0.585
Inspiratory time, <i>sec</i>	1.1 (0.8–1.8)	1.2 (0.9–2.1)	0.003	1.2 (1.0–1.9)	1.2 (1.1–1.9)	0.499	1.2 (1.0–2.0)	1.2 (1.0–2.0)	0.402
Peak airway pressure, <i>cmH₂O</i>	19 (15–24)	25 (19–31)	<0.0001	19 (15–24)	19 (15–24)	0.530	19 (15–24)	19 (15–24)	0.861
<i>Blood gases</i>									
pH	7.47 (7.45–7.50)	7.47 (7.44–7.41)	0.623	7.47 (7.43–7.50)	7.47 (7.43–7.50)	0.589	7.47 (7.42–7.50)	7.47 (7.41–7.50)	0.226
PaO ₂ , <i>mmHg</i>	72 (63–94)	72 (60–88)	0.759	80 (67–93)	77 (68–93)	0.046	78 (68–98)	81 (62–95)	0.529
PaCO ₂ , <i>mmHg</i>	40 (36–45)	44 (34–45)	0.905	43 (37–44)	41 (35–45)	0.733	44 (37–45)	43 (37–46)	0.572
SaO ₂ , %	95 (92–97)	96 (90–97)	0.725	97 (93–98)	96 (93–98)	0.031	97 (93–98)	96 (91–98)	0.07
HCO ³⁻ , <i>mmol/L</i>	29 (28–32)	29 (27–32)	0.409	31 (28–32)	29 (28–32)	0.344	30 (27–32)	29 (27–32)	0.09
<i>Hemodynamic pattern</i>									
Heart rate, min^{-1}	99 (91–115)	93 (78–104)	<0.0001	102 (93–113)	93 (81–103)	<0.0001	106 (94–113)	93 (86–105)	<0.0001
Mean blood pressure, <i>mmHg</i>	84 (78–90)	86 (76–94)	0.884	84 (77–90)	82 (75–90)	0.261	82 (76–91)	82 (78–94)	0.210

Data are expressed as median (interquartile range)

FIGURES

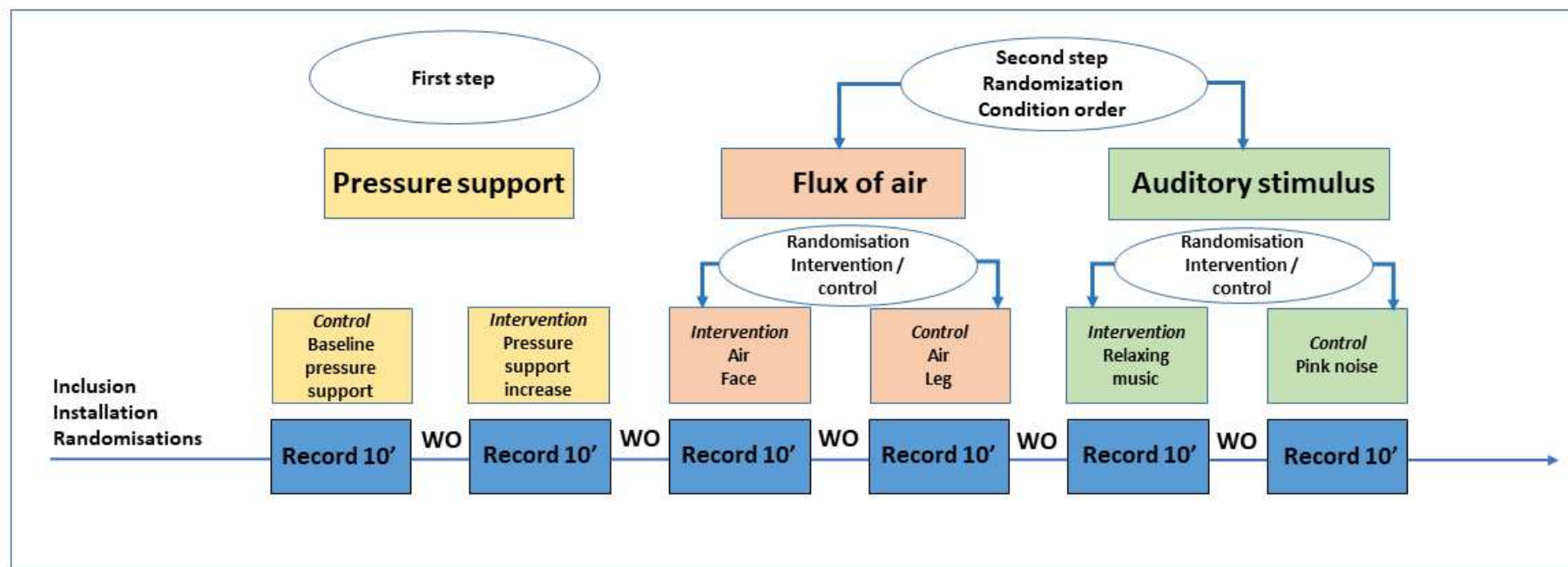


Figure 1. Experimental design

WO, washout.

The first step consisted of “Baseline pressure support” and “pressure support increase” conditions. During the second step, two randomisations were carried out to define 1) the order of administration of the Air flux and Auditory stimulus, 2) for each of the two stimulations, the order of administration of the "intervention" and "control" conditions.

The duration of the washout was 10 minutes. Ventilatory parameters were unchanged during all conditions except for the 5 cmH₂O pressure support increase, which was limited to the duration of the PS-Increase condition.

"Pressure support increase" was performed in patients #15 to #46 only, after filing a protocol amendment.

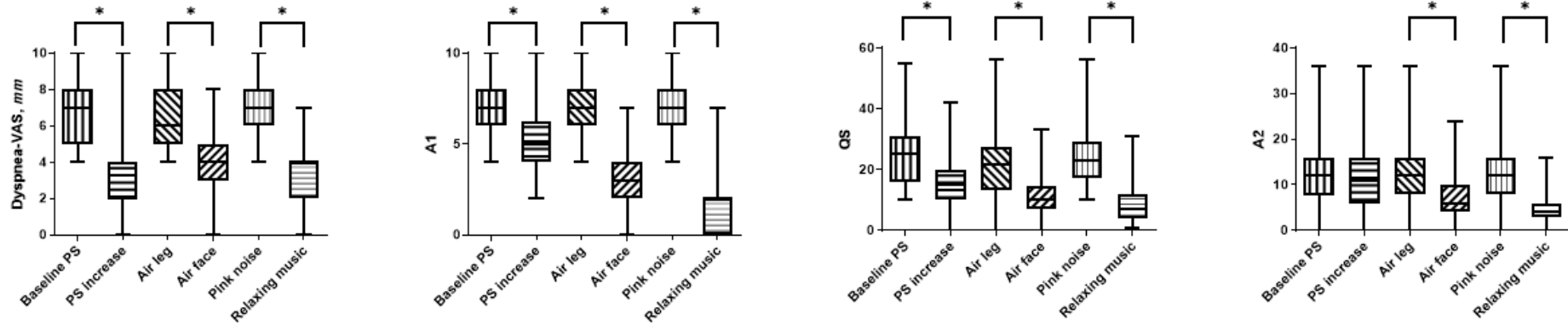


Figure 2. Unidimensional dyspnea visual analogue scale (Dyspnea-VAS) and A1, QS, A2 of the Multidimensional Dyspnea Profile questionnaire during pressure support, flux of air, and auditory stimulus

*Line inside the boxes is median, limits of the boxes are 75th and 25th percentiles of the data (interquartile range), whiskers are 5th and 95th percentiles. *p<0.05*

Dyspnea-VAS, dyspnea visual analogue scale; A1, dyspnea affective score; QS, dyspnea sensory score; A2, dyspnea emotional score; PS, pressure support.

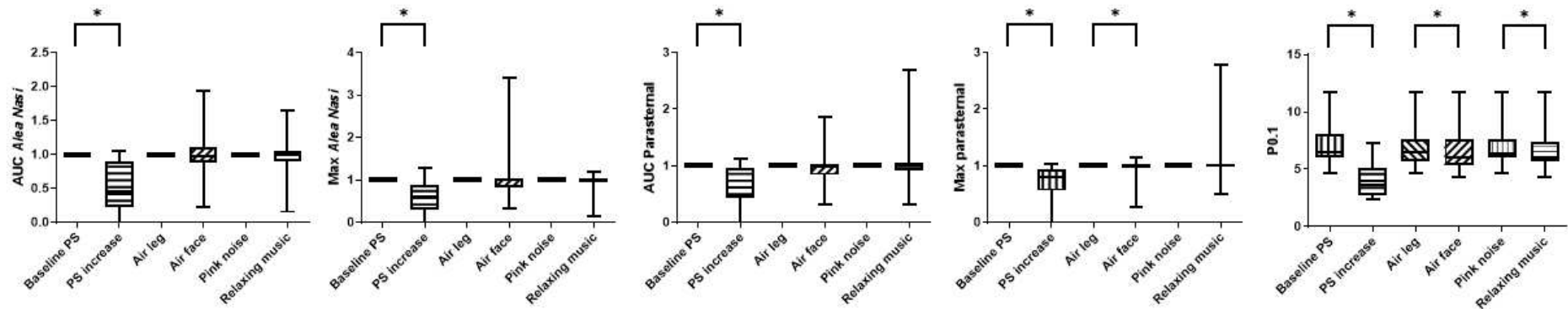


Figure 3. Electromyographic (EMG) activity of *Alae nasi* and parasternal intercostal muscles and occlusion pressure (P0.1) during pressure support increase, flux of air, and auditory stimulus

The EMG activity is described by peak EMG (EMGmax) and area under the curve (EMGauc) and is expressed as a proportion of the EMG activity under the control condition (either Baseline PS, Air leg, or Pink noise).

Line inside the boxes is median, *limits of the boxes* are 75th and 25th percentiles of the data (interquartile range), *whiskers* are 5th and 95th percentiles.

*p<0.05

PS, pressure support.

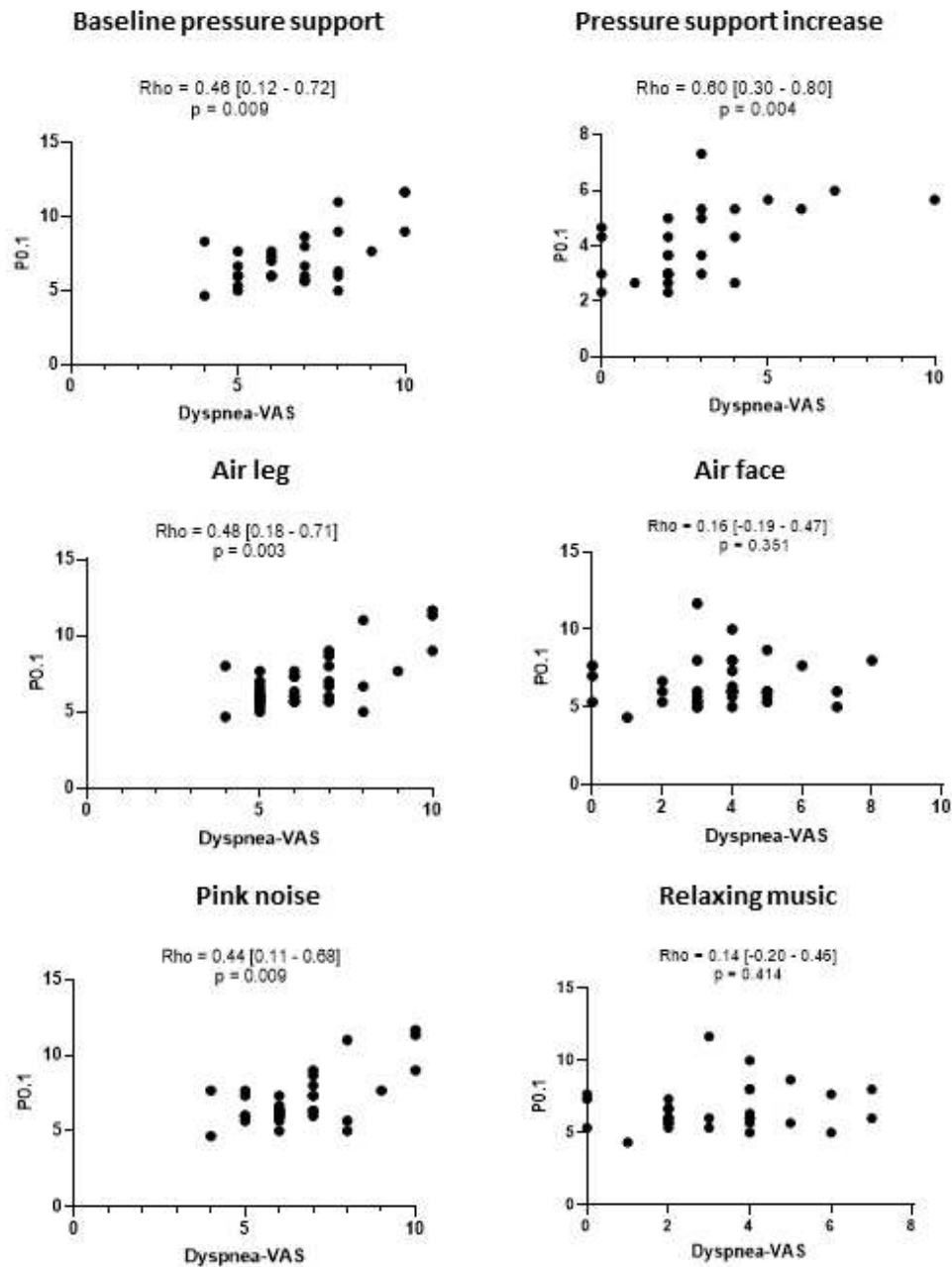


Figure 4. Correlation between occlusion pressure (P0.1) and the unidimensional dyspnea-visual analogue scale (Dyspnea-VAS) during pressure support increase, flux of air, and auditory stimulus

Sensory interventions to relieve dyspnea in critically ill mechanically ventilated patients

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Supplemental Table S4. Dyspnea, electromyographic activity, and P0.1 during pressure support increase, flux of air, and auditory stimulus control in the intubated population

Supplemental Table S5. Dyspnea, electromyographic activity, and P0.1 during pressure support increase, flux of air, and auditory stimulus in the population under non-invasive ventilation

Supplemental Methods 1. Detailed description of the Multidimensional Dyspnea Profile questionnaire

The MDP questionnaire was presented to the patient as follows: “This questionnaire is designed to help us understand how you perceive and feel about your breathing. There are no right or wrong answers. We want to know what you have to say about your breathing. First, we will ask you how uncomfortable you find your breathing. Then we will talk about the intensity (strength) of your breathing sensations. To help you differentiate between unpleasantness and intensity, imagine that you are listening to music, for example on the radio. As the sound increases, it may become more or less unpleasant. The intensity of the sensation corresponds to the volume of the sound. Regarding the unpleasantness, this can appear when the sound increases or can exist even if the sound is low. For example, music that you dislike will be unpleasant even if the volume is low and will become more and more unpleasant as the volume increases. On the other hand, music that you like will remain pleasant even if it is loud”.

- **A1 scale (affect):** Use this scale to assess the unpleasantness or discomfort of your breathing sensations. Zero corresponds to "neither pleasant nor annoying"; 10 corresponds to "unbearable".
- **Choice QS:** Rate on the following scale the intensity of the breathing sensations you experience (whether they were pleasant or unpleasant [remember that a sensation like music can be strong without being unpleasant]). Zero corresponds to "I did not experience this sensation"; 10 corresponds to "the highest intensity imaginable".
 - I have to work *or* make a muscular effort to breathe
 - I am short of air *or* I am suffocating *or* I feel that I need air
 - I feel that my chest and lungs are tight *or* compressed.
 - I have to concentrate *or* make a mental effort to breathe

- I breathe hard

All patients were asked if they wished to add additional descriptions of their breathing sensations if necessary.

- **A2 scale (affect):** When you feel that you are not breathing normally, you may be experiencing emotions or "feelings. Using the following scales that I will explain to you, please indicate how you felt about your breathing sensations - mark zero for feelings that you do not experience. Zero is "I did not experience this feeling"; 10 is "I experienced this feeling in the worst way imaginable".

- Do you feel depressed?
- Do you feel anxious?
- Do you feel frustrated?
- Do you feel angry?
- Do you feel frightened?

Supplemental Methods 2. Detailed measurement of the verbatim report

Patients were asked to express their feelings after receiving the two extra-breathing stimuli (Air-Face and Relaxing Music) which were reported verbatim. Patients who could not speak because of mechanical ventilation were asked to write words or short sentences on a slate with a felt pen and then to choose three words representing their feelings. The chosen words were translated into English using software (Deepl, Cologne, Germany) and presented as a word cloud using online software (nuagedemots.co, La Roche sur Foron, France). The size of the word presented in the word cloud is proportional to the frequency of usage of the word.

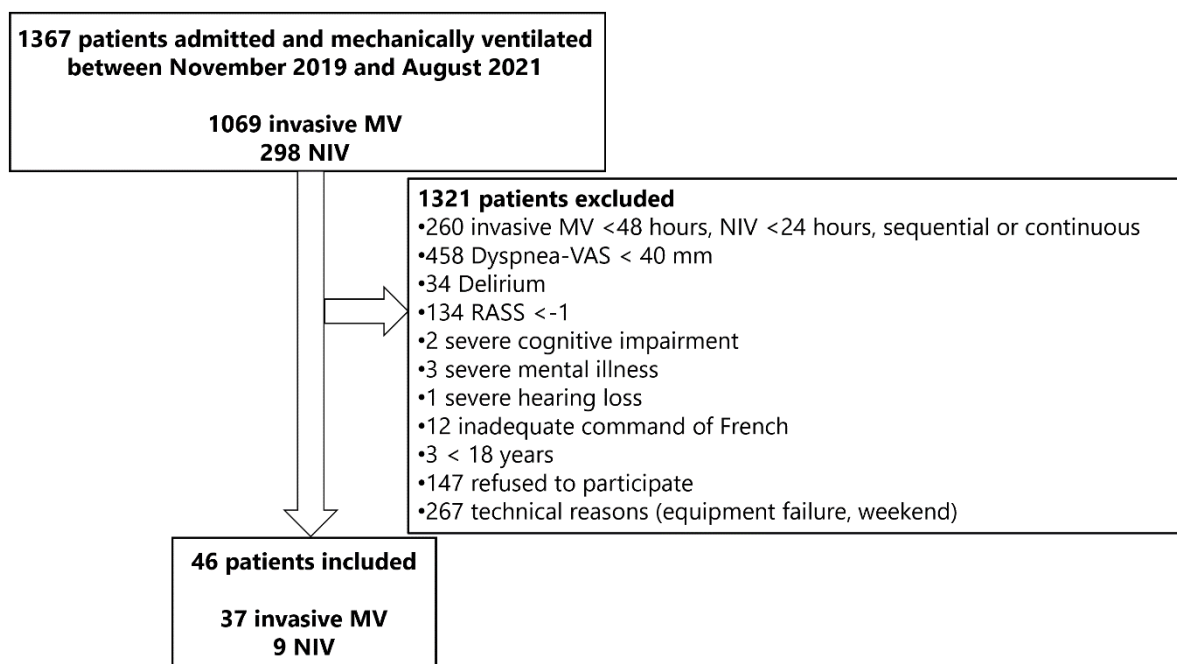
Supplemental Methods 3. Detailed measurement and data analysis of electromyography (EMG) of inspiratory muscles (parasternal intercostal muscle and *Alea nasi*)

Measurement

The EMG signal was collected by self-adhesive surface electrodes similar to those commonly used to record electrocardiograms in critically ill patients, with an interval of 2 cm between the two electrodes. Electrode positions varied according to the muscle recorded. For EMG of the parasternal intercostal muscles, electrodes were placed next to the second intercostal space as close as possible to the sternum. For EMG of the *Alea nasi* muscles, electrodes were placed on the lateral surfaces of the nose (nostrils) (1). EMG signals were amplified, sampled at a frequency of 10 kHz, and finally filtered between 40 and 500 Hz (PowerLab, AD Instruments, Hastings, UK).

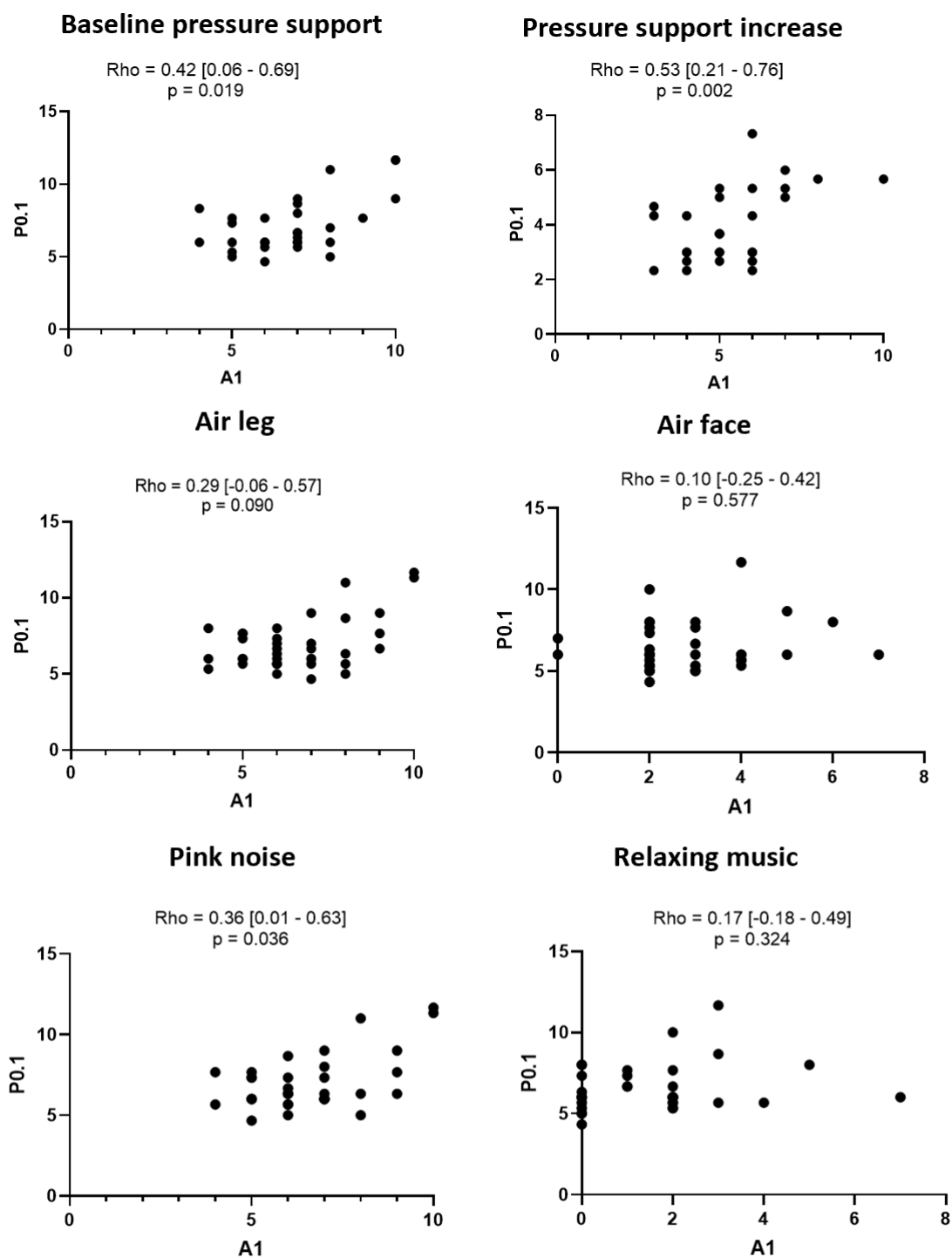
Data analysis

Inspiratory muscle EMG activity, used to estimate respiratory drive, was processed using the Labchart Peak Analysis module MLS380/8 (ADInstruments, Dunedin, New Zealand). This module generated a Root Mean Square (RMS) of the EMG that was used to measure the maximum amplitude of the EMG signal (EMG_{max}), defined by the difference between the maximum amplitude of the RMS signal and its baseline, and the area under the curve of the EMG signal (EMG_{auc}), calculated by integration of the RMS between its deflection from the baseline and its return to this same baseline. EMG_{max} and EMG_{auc} were expressed as a proportion of the activity measured under the control condition.

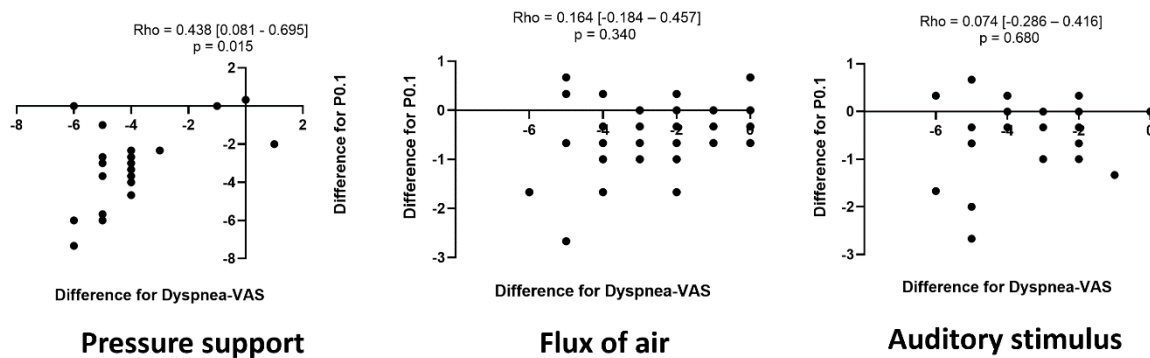
Supplemental Figure S1. Study flow-chart

MV, mechanical ventilation; NIV, non-invasive ventilation; RASS, Richmond agitation and sedation scale; Dyspnea-VAS, dyspnea visual analogue scale

Supplemental Figure S2. Correlation between P0.1 and the A1 affective score of the Multidimensional Dyspnea Profile questionnaire during pressure support increase, flux of air and auditory stimulus



Supplemental Figure S3. Correlation between difference between intervention and control condition for P0.1 and difference between intervention and control condition for Dyspnea visual analogic scale (Dyspnea-VAS) during pressure support increase, flux of air and auditory stimulus



The difference for P0.1 and Dyspnea-VAS is calculated between the PS-Increase and PS-Baseline conditions.

Supplemental Figure S4. Word cloud of feelings after air face stimulation



Supplemental Table S1. Dyspnea-Visual analogue scale and French version of the Multidimensional Dyspnea Profile (MDP) questionnaire during pressure support increase, flux of air and auditory stimulus

	<i>Pressure Support</i>			<i>Flux of air</i>			<i>Auditory Stimulus</i>		
	PS-Baseline	PS-Increase	p	Air-Leg	Air-Face	p	Pink-Noise	Relaxing-Music	p
Dyspnea-VAS, mm	70 (60 – 80)	20 (20 – 40)	< 0.0001	60 (50 – 80)	40 (30 – 50)	< 0.0001	70 (60 – 80)	40 (20 – 40)	< 0.0001
MDP A1 affective score	7 (6 – 8)	5 (4 – 6)	< 0.0001	7 (6 – 8)	3 (2 – 4)	< 0.0001	7 (6 – 8)	2 (0 – 2)	< 0.0001
MDP QS sensory score	25 (15 – 31)	15 (10 – 20)	< 0.0001	21 (13 – 27)	10 (7 – 15)	< 0.0001	20 (14 – 27)	6 (4 – 12)	< 0.0001
MDP A2 emotional score	12 (7 – 16)	11 (6 – 16)	0.174	12 (8 – 16)	6 (4 – 10)	< 0.0001	12 (8 – 16)	4 (3 – 6)	< 0.0001
Immediate perception domain (A1 + QS)	32 (22 – 38)	20 (14 – 27)	< 0.0001	29 (23 – 36)	14 (10 – 20)	< 0.0001	29 (24 – 35)	9 (6 – 15)	< 0.0001
Affective dimension (A1 + A2)	20 (12 – 25)	16 (11 – 22)	< 0.0001	19 (13 – 23)	9 (7 – 12)	< 0.0001	19 (13 – 23)	6 (4 – 9)	< 0.0001
MDP physical breathing effort	5 (0 – 6)	4 (0 – 5)	< 0.0001	5 (3 – 6)	2 (1 – 4)	< 0.0001	5 (3 – 7)	2 (0 – 3)	< 0.0001
MDP air hunger	6 (3 – 8)	4 (1 – 5)	< 0.0001	6 (3 – 7)	3 (1 – 4)	< 0.0001	6 (4 – 7)	2 (0 – 4)	< 0.0001
MDP tightness	5 (1 – 6)	3 (1 – 4)	< 0.0001	5 (2 – 6)	2 (0 – 4)	< 0.0001	5 (0 – 6)	2 (0 – 3)	< 0.0001
MDP mental breathing effort	4 (0 – 5)	2 (0 – 3)	0.001	3 (0 – 5)	1 (0 – 3)	0.001	3 (0 – 5)	0 (0 – 2)	< 0.0001
MDP hyperpnoea	6 (5 – 8)	4 (2 – 6)	< 0.0001	6 (5 – 7)	2 (2 – 4)	< 0.0001	6 (5 – 7)	2 (0 – 3)	< 0.0001
MDP depressed	4 (2 – 6)	4 (2 – 5)	0.346	3 (2 – 5)	2 (1 – 3)	< 0.0001	4 (2 – 5)	2 (0 – 2)	< 0.0001
MDP anxious	4 (2 – 6)	4 (2 – 5)	0.341	4 (2 – 6)	2 (2 – 4)	< 0.0001	4 (2 – 6)	2 (2 – 3)	< 0.0001
MDP frustrated	0 (0 – 0)	0 (0 – 0)	0.987	0 (0 – 0)	0 (0 – 0)	0.685	0 (0 – 0)	0 (0 – 0)	0.845
MDP angry	0 (0 – 0)	0 (0 – 0)	0.895	0 (0 – 0)	0 (0 – 0)	0.912	0 (0 – 0)	0 (0 – 0)	0.495
MDP frightened	4 (0 – 6)	4 (0 – 5)	0.018	4 (0 – 5)	2 (0 – 3)	< 0.0001	4 (0 – 5)	2 (0 – 2)	< 0.0001

Dyspnea-VAS Dyspnea Visual analogue scale; A1 Affective score; QS Sensory score; A2 Emotional score; MDP Multidimensional Dyspnea Profile

Supplemental Table S2. Difference between intervention and control condition for dyspnea-visual analogue scale (Dyspnea-VAS), Multidimensional Dyspnea Profile (MDP) questionnaire and P0.1 during pressure support increase, flux of air and auditory stimulus

	<i>Pressure support</i> PS-increase – PS-Baseline	<i>Flux of Air</i> Air-Face – Air-Leg *	<i>Auditory stimulus</i> Relaxing-Music – Pink noise	p
Dyspnea-VAS, mm	-40 (-50 – -40)	-30 (-40 – -20) *	-40 (-50 – -30)	0.001
MDP A1 affective score	-2 (-3 – -1)	-7 (-4 – -11) *	-5 (-7 – -4) *\$	<0.0001
MDP QS sensory score	-8 (-12 – -6)	-11 (-14 – -7) *	-13 (-19 – -9) *\$	<0.0001
MDP A2 emotional score	0 (-1 – 0)	-4 (-8 – -2) *	-7 (-5 – -3) *\$	<0.0001
MDP physical breathing effort	-1 (-2 – 0)	-2 (-3 – 0)	-3 (-4 – 0) *	<0.0001
MDP air hunger	-2 (-3 – 0)	-2 (-4 – 0)	-3 (-4 – 0) *	<0.0001
MDP tightness	-1.5 (-3 – 0)	-2 (-3 – 0)	-3 (-4 – 0) *	0.001
MDP mental breathing effort	0 (-2 – 0)	-1 (-3 – 0)	-1 (-4 – 0)	0.007
MDP hyperpnoea	-2 (-4 – -1.75)	-3 (-4 – -2)	-4 (-5 – -3)	0.041
MDP depressed	0 (0 – 0)	-1 (-2 – 0) *	-1 (-4 – 0) *	<0.0001
MDP anxious	0 (0 – 0)	-1 (-2 – 0) *	-2 (-4 – 0) *	<0.0001
MDP frustrated	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.0244
MDP angry	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.014
MDP frightened	0 (0 – 0)	-2 (-3 – 0) *	-2 (-4 – 0) *	<0.0001
P0.1	-3.3 (-3.7 – -2.3)	-0.3 (-0.9 – 0) *	-0.3 (-1.0 – 0) *	<0.0001

PS Pressure Support; Dyspnea-VAS Dyspnea Visual analogue scale; A1 Affective score; QS Sensory score; A2 Emotional score; MDP Multidimensional Dyspnea Profile

* p <0.05 compared to the Incrementation condition, \$ p <0.05 compared to the Sensory condition

Supplemental Table S3. Dyspnea, electromyographic activity and P0.1 during pressure support increase, flux of air and auditory stimulus in the tracheotomized population

	<i>Pressure Support</i>			<i>Flux of air</i>			<i>Auditory Stimulus</i>		
	PS-Baseline	PS-Increase	p	Air-Leg	Air-Face	p	Pink-Noise	Relaxing-Music	p
<i>Dyspnea</i>									
Dyspnea-VAS, mm	65 (50 – 80)	20 (0 – 40)	0.001	60 (50 – 72)	35 (17 – 42)	0.001	60 (50 – 75)	20 (15 – 40)	0.001
MDP A1 affective score	7 (5 – 8)	5 (4 – 6)	0.003	6 (6 – 8)	2 (2 – 3)	0.001	6 (5 – 7.5)	2 (0 – 2)	0.001
MDP QS sensory score	21 (14 – 32)	14 (8 – 21)	0.001	20 (14 – 31)	8 (4 – 14)	0.001	20 (15 – 30)	7 (4 – 14)	0.001
MDP A2 emotional score	12 (4 – 15)	11 (4 – 15)	0.270	12 (5 – 15)	6 (4 – 10)	0.001	12 (6 – 15)	4 (4 – 6)	0.001
<i>Electromyography</i>									
Alea Nasi EMGmax	1 (1-1)	0.42 (0.38-0.88)	0.001	1 (1-1)	1.00 (0.97-1.01)	0.839	1 (1-1)	0.98 (0.73-1.04)	0.177
Alea Nasi EMGauc	1 (1-1)	0.45 (0.23-0.92)	0.001	1 (1-1)	0.97 (0.90-1.13)	1	1 (1-1)	0.97 (0.68-1.03)	0.118
Parasternal EMGmax	1 (1-1)	0.85 (0.81-0.96)	0.001	1 (1-1)	0.99 (0.98-1.06)	1	1 (1-1)	1.00 (0.96-1.01)	0.614
Parasternal EMGauc	1 (1-1)	0.75 (0.36-0.96)	0.001	1 (1-1)	0.99 (0.83-1.06)	0.485	1 (1-1)	1.01 (0.92-1.12)	0.896
<i>P0.1</i>									
P0.1	6.2 (5.5 – 7.8)	6.0 (5.7 – 7.4)	0.002	6.5 (5.7 – 7.4)	5.8 (5.2 – 7.1)	0.002	6.3 (5.8 – 7.5)	6.0 (5.3 – 7.3)	0.030

PS Pressure Support; Dyspnea-VAS Dyspnea Visual analogue scale; A1 Affective score; QS Sensory score; A2 Emotional score; MDP Multidimensional Dyspnea Profile

Supplemental Table S4. Dyspnea, electromyographic activity and P0.1 during pressure support increase, flux of air and auditory stimulus control in intubated population

	<i>Pressure Support</i>			<i>Flux of air</i>			<i>Auditory Stimulus</i>		
	PS-Baseline	PS-Increase	p	Air-Leg	Air-Face	p	Pink-Noise	Relaxing-Music	p
<i>Dyspnea</i>									
Dyspnea-VAS, mm	65 (52 – 77)	20 (20 – 30)	<0.0001	60 (50 – 70)	40 (30 – 50)	<0.0001	60 (60 – 70)	40 (20 – 40)	<0.0001
MDP A1 affective score	7 (6 – 7.5)	5 (4 – 6)	0.004	6 (5 – 8)	3 (2 – 4)	<0.0001	6 (5 – 7.5)	2 (0 – 2)	<0.0001
MDP QS sensory score	25 (17 – 27)	15 (12 – 18)	<0.0001	24 (15 – 26)	11 (9 – 14)	<0.0001	24 (17.5 – 27)	6 (4 – 11)	<0.0001
MDP A2 emotional score	13 (8 – 19)	11.5 (8 – 19)	0.25	13 (9 – 17)	7.5 (5.5 – 10)	<0.0001	12 (8.5 – 18)	4 (2.5 – 6)	<0.0001
<i>Electromyography</i>									
Alea Nasi EMGmax	1 (1-1)	0.61 (0.28-0.85)	<0.0001	1 (1-1)	0.98 (0.78-1.01)	0.021	1 (1-1)	0.99 (0.97-1.00)	0.105
Alea Nasi EMGauc	1 (1-1)	0.42 (0.23-0.80)	<0.0001	1 (1-1)	0.99 (0.79-1.01)	0.542	1 (1-1)	1.00 (0.96-1.07)	0.678
Parasternal EMGmax	1 (1-1)	0.64 (0.53-0.80)	<0.0001	1 (1-1)	0.99 (0.79-1.00)	0.012	1 (1-1)	0.99 (0.95-1.04)	0.988
Parasternal EMGauc	1 (1-1)	0.60 (0.43-0.73)	<0.0001	1 (1-1)	0.97 (0.82-1.02)	0.115	1 (1-1)	0.97 (0.90-1.01)	0.118
<i>P0.1</i>									
P0.1	7.0 (6.0 – 8.5)	3.0 (5.7 – 5.3)	<0.0001	6.7 (5.9 – 8.2)	6.0 (5.9 – 8)	0.04	6.3 (6.0 – 8.3)	6.0 (5.8 – 7.8)	0.03

PS Pressure Support; Dyspnea-VAS Dyspnea Visual analogue scale; A1 Affective score; QS Sensory score; A2 Emotional score; MDP Multidimensional Dyspnea Profile

Supplemental Table S5. Dyspnea, electromyographic activity and P0.1 during pressure support increase, flux of air and auditory stimulus in population under non-invasive ventilation

	<i>Pressure Support</i>			<i>Flux of air</i>			<i>Auditory Stimulus</i>		
	PS-Baseline	PS-Increase	p	Air-Leg	Air-Face	p	Pink-Noise	Relaxing-Music	p
<i>Dyspnea</i>									
Dyspnea-VAS, mm	80 (57 – 95)	40 (22 – 50)	0.125	80 (80 – 80)	40 (40 – 50)	0.015	80 (70 – 80)	40 (30 – 40)	0.003
MDP A1 affective score	9 (6.5 – 10)	7 (3 – 8)	0.125	9 (7 – 10)	4 (4 – 4)	0.015	7 (6 – 9)	2 (0 – 3)	0.004
MDP QS sensory score	34 (19– 50)	23 (13 – 38)	0.125	26 (19 – 37)	16 (8 – 20)	0.015	20 (18 – 32)	9 (6 – 15)	0.004
MDP A2 emotional score	10 (6 – 29)	7 (4 – 28)	0.500	11 (6 – 24)	6 (3 – 14)	0.031	12 (6 – 19)	6 (2 – 8)	0.004
<i>Electromyography</i>									
Parasternal EMGmax	1 (1-1)	0.80 (0.55-0.98)	0.125	1 (1-1)	0.97 (0.85-0.99)	0.156	1 (1-1)	0.99 (0.99-1.35)	0.641
Parasternal EMGauc	1 (1-1)	0.76 (0.48-0.97)	0.125	1 (1-1)	0.97 (0.87-1.15)	0.937	1 (1-1)	1.03 (0.99-1.27)	0.250

PS Pressure Support; Dyspnea-VAS Dyspnea Visual analogue scale; A1 Affective score; QS Sensory score; A2 Emotional score; MDP Multidimensional Dyspnea Profile

Increasing sweep gas flow through the membrane lung reduces respiratory drive and dyspnea in veno-arterial ECMO patients

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Abstract (n = 242)

Introduction. Data on dyspnea in patients on veno-arterial extracorporeal membrane oxygenation (vaECMO) for cardiogenic shock are lacking. Our objective was to evaluate, in vaECMO patients exhibiting significant dyspnea, the impact of an increase in sweep gas flow through the vaECMO membrane on dyspnea and respiratory drive.

Methods. Patients with vaECMO for cardiogenic shock who presented a dyspnea ≥ 40 mm/100 on a visual analog dyspnea scale (dyspnea-VAS) were included. Sweep gas flow was increased up to +6 L/min by three steps of +2 L/min each. Dyspnea was assessed with the dyspnea-VAS and the Multidimensional Dyspnea Profile. The respiratory drive was assessed by the electromyographic activity of the *Alea Nasi* and parasternal muscles.

Results. We included 21 non-mechanically ventilated patients. On inclusion, median dyspnea-VAS was 50 ([interquartile range] 45–60) mm and sweep gas flow was 1.0 L/min (0.5–2.0). Increased in sweep gas flow decreased significantly respiratory rate ($p < 0.0001$), PaCO₂ ($p < 0.01$), the electromyographic activity of *Alea nasi* and parasternal muscles ($p < 0.001$) and dyspnea-VAS ($p < 0.0001$). The decrease in dyspnea was greater for the sensory component of dyspnea (-50% [43-75]) than for the affective component (-17% [0-25] and -12% [0-17], $p < 0.001$). There was a significant correlation between the respiratory drive and the sensory component of dyspnea (Rho 0.33, $p = 0.006$), but not the affective component of dyspnea.

Conclusion. In critically ill patients with vaECMO, an increase in sweep gas flow through the oxygenation membrane decreases dyspnea, probably mediated by a decrease in respiratory drive.

Introduction

There is an increasing body of knowledge showing that dyspnea, the symptom of respiratory-related brain suffering, is frequent in mechanically ventilated patients, either invasive or non-invasive ventilation¹⁻³. When present, dyspnea is severe and reaches levels that would require an immediate therapeutic response in the case of pain¹⁻⁴. Dyspnea is one of the worst ICU-related recollections that patients report and is associated with anxiety and the fear of death. Moreover, dyspnea is associated with a higher prevalence of post-traumatic stress disorder². Relieving dyspnea in intensive care unit (ICU) patients should be a major therapeutic goal for every physician and for this it is important to understand the underlying mechanisms of dyspnea and its relief^{5,6}.

Veno-arterial extracorporeal membrane oxygenation (vaECMO) is increasingly used to treat cardiogenic shock⁷. Moreover, awake vaECMO (i.e without invasive mechanical ventilation) is now part of current practices as it may be associated with improved short- and long-term outcomes⁸. Thus, patients on vaECMO are highly exposed to dyspnea which could be secondary to cardiogenic pulmonary edema⁹. To date, information on dyspnea and dyspnea relief in patients on vaECMO are lacking.

Dyspnea relates with the respiratory drive¹⁰, in turn related with the respiratory system load capacity balance^{11,12}. Carbon dioxide (CO₂) increases chemical loading and is in turn a powerful stimulus of the respiratory drive. It elicits dyspnea independently of the contraction of the respiratory muscles^{13,14}. Veno-arterial ECMO offers the opportunity to mitigate the arterial partial pressure in CO₂ (PaCO₂) by varying the sweep gas flow through the ECMO membrane independently of the breathing pattern. Increasing the flow of the sweep gas flow through an oxygenation membrane, this time studied in patients on veno-venous ECMO, decreases respiratory drive, but its impact on dyspnea has not been evaluated¹⁵⁻¹⁷.

Given all these observations, we hypothesized that the modulation of the sweep gas flow through the vaECMO membrane may relieve dyspnea in non-intubated vaECMO patients exhibiting clinically significant dyspnea, with a parallel reduction of the respiratory drive.

Patients and methods

This interventional, single-center prospective study was performed in the 28-bed medical intensive care unit (ICU) of the Cardiology Institute of APHP Sorbonne Université - La Pitié-Salpêtrière hospital, Paris, France.

Patients

The study was approved by the *Comité de Protection des Personnes Ile de France VI* (N. CPP/35-13) and the *Comité de Protection des Personnes Ouest III* (N. 20.04.25). Informed consent was obtained from patients.

Patients were eligible as soon as they met the following criteria: 1) cardiogenic shock supported by vaECMO, 2) on spontaneous ventilation, 3) dyspnea ≥ 40 mm on a visual dyspnea analogic scale (dyspnea-VAS) from 0 ("no respiratory discomfort") to 100 ("worst imaginable respiratory discomfort"), 4) decision by the physician in charge of the patient to increase the vaECMO sweep gas flow to relieve dyspnea, 5) communicative patient, , able to reliably self-report dyspnea, defined by Richmond Agitation-Sedation Scale between 0 and +1, absence of delirium as assessed by the CAM-ICU, no severe cognitive impairment, no severe mental illness or severe hearing loss, speak French, and able to execute the five following orders: open and close eyes, look at examiner, nod, open mouth and stick out tongue, raise eyebrows at examiner's count of five.

Exclusion criteria were: 1) central ECMO, left ventricular assist or long-term bi-ventricular assist, 2) age <18 years, known pregnancy, legal guardianship.

Measurements

Anthropometric data, medical history and current treatments were collected at inclusion. The parameters of vaECMO : inspired oxygen fraction, blood flow, rotation per minute, sweep gas flow, and cannula location were collected at inclusion. Physiological variables (respiratory rate, heart rate and mean blood pressure) were collected after each scan increment.

Pulmonary edema quantification. The computerized chest radiograph closest to the day of inclusion was analyzed. Pulmonary edema was quantified using the Weinberg radiological score^{18,19}. Chest X-rays were divided into four quadrants, each quantified as: 0, normal; 1, interstitial infiltrate; 2, non-confluent infiltrate; 3, condensation; then the four quadrant values were added. A Weinberg score greater than 4 defined radiological pulmonary edema.

Quantification of dyspnea. Dyspnea was quantified by the dyspnea-VAS for the intensity and was also assessed by the French version of the Multidimensional Dyspnea Profile (MDP) questionnaire, which is composed of one affective score (A1), one sensory score (QS) and one emotional score (A2). Briefly, The A1 score assesses the unpleasantness of respiratory discomfort using an ordinal scale ranging from 0 (“neither pleasant nor annoying”) to 10 (“unbearable”). The QS score assesses five sensory traits (physical breathing effort, air hunger, tightness, mental breathing effort, and hyperpnea) with an ordinal scale from 0 to 10 (0 corresponding to the absence of the sensation and 10 corresponding to the highest imaginable intensity). The A2 score assesses five emotions (depressed, anxious, angry, frustrated, and afraid) with an ordinal scale from 0 to 10 (0 corresponding to the absence of the emotion and 10 corresponding to the highest imaginable intensity). The maximum score for A1 is 10 and 50 for QS and A2. A detailed description of the MDP questionnaire, how questions were asked to patients, and how the three scores were computed is provided in the supplement ([Supplemental data 1](#)).

Electromyography (EMG) of extradiaphragmatic inspiratory muscles. The amplitude of the extradiaphragmatic inspiratory muscles’ EMG signal is a surrogate for central respiratory

drive and is proportional to dyspnea intensity ^{20,21}. The EMG signal was collected by self-adhesive surface electrodes like those commonly used to record the electrocardiogram signal in critically ill patients, with an interval of 2 cm between the two electrodes. For EMG of the parasternal intercostal muscles, electrodes were placed next to the second intercostal space as close as possible to the sternum. For EMG of the *Alae nasi* muscles, electrodes were placed on the lateral surfaces of the nose (nostrils) ¹⁰. EMG signals were amplified, sampled at a frequency of 10 kHz, and finally filtered between 40 and 500 Hz (PowerLab, AD Instruments, Hastings, UK).

Arterial blood gases. Blood gases were sampled at the end of each condition using an arterial catheter.

Study design

The flow of sweep gas through the lung membrane was increased by steps of 2l/min. After, each increase in sweep gas flow, a five-minute stabilization period was allowed, before dyspnea was quantified, physiological variables were reported, blood gas was sampled and 10-min extradiaphragmatic inspiratory muscles EMG was obtained.

Data analysis

Electromyogram (EMG) of extradiaphragmatic inspiratory muscles. Inspiratory muscle EMG activity was processed using the Labchart Peak Analysis module MLS380/8 (ADInstruments, Dunedin, New Zealand). This module generated a root mean square of the EMG that was used to measure the maximum amplitude of the EMG signal (EMGmax), defined by the difference between the maximum amplitude of the root mean square signal and its baseline, and the area under the EMG signal curve (EMGauc), calculated by integration of the root mean square between its deflection from the baseline and its return to this same baseline. EMGmax and EMGauc were expressed as a proportion of the activity measured under the control condition.

Statistical analysis

Statistical analysis were performed with Prism 8.0 software (GraphPad Software, USA). Quantitative variables were described by their median and interquartile interval. Qualitative variables were expressed in absolute value and percentage. All analyses were performed with a type I error of 5%. Continuous variables were compared using a Friedman test, followed, when positive, by a *post hoc* comparison using a Dunn multiple comparison test. Correlations between variables were evaluated using the Spearman rank correlation coefficient.

For sample size calculation, we expected that interventions would reduce dyspnea by 25% according to baseline, according to previous reports²². Given the fact that median dyspnea-VAS is 50 mm in dyspneic mechanically ventilated patients, this corresponded to a reduction of dyspnea by 12.5 mm, which is more than the minimally clinically important difference (10 mm) for Dyspnea-VAS in other clinical contexts²³. With a power of 0.9, a sample size of 30 patients was expected.

Results

Between August 2020 and August 2021, 48 patients with vaECMO had a dyspnea-VAS ≥ 4 . Among them, one patient was younger than 18 years, four were noncommunicative and could not reliably self-report dyspnea, five had RASS >1 , six refused to participate and 11 patients were not included for a technical reason (equipment failure, weekend). Eventually, 21 patients were included in the study. Patient characteristics and vaECMO settings on inclusion are reported in **Table 1**. All patients were concomitantly equipped with an Intra-Aortic Balloon Pump. Weinberg radiological pulmonary edema score was 3 (0-5); the chest X-ray used for the score was taken within 24 hours of inclusion for all patients..

Clinical parameters and blood gas

Sweep gas flow, physiological parameters and blood gases at baseline and after each increment of sweep gas flow are reported in [Table 2](#). The sweep gas flow at inclusion was 1.0 L/min (0.5-2.0). PaCO₂ decreased in response to the +4 L/min increase in sweep gas flow (p=0.004). Similarly, the respiratory rate decreased in response to the +4 L/min increase in sweep gas flow (p<0.0001).

Dyspnea

Dyspnea-VAS and the A1, QS and A2 components of the MDP at baseline and after each increment of sweep gas flow are reported in [Figure 1](#). Detailed MDP questionnaire at baseline and after each increment of sweep gas flow is reported in [Table 3](#). At baseline, dyspnea-VAS was 50 mm (45-60). dyspnea-VAS and QS (sensory dimension of the MDP) decreased in response to the 4 L/min increase in sweep gas flow (p<0.0001). The A1 (respiratory discomfort), and A2 (emotional response) components of the MDP decreased in response to the 6 L/min increase in sweep gas flow (p<0.0001).

In seventeen out of twenty-one patients (81%) the dyspnea-VAS decreased by at least 50% between the basal condition and the +6 L/min condition. The percentages of reduction between the basal condition and the +6 L/min condition was -67% (50-80) for dyspnea-VAS, -50% (43-75) for QS, -17% (0-25) for A1 and -12% (0-17) for A2 scores. The reduction of QS was significantly higher than the reduction of A1 and A2 (p < 0.0001 and p < 0.001, respectively).

Extradiaphragmatic inspiratory muscle EMG activity

Electromyographic activity of *Alae nasi* and parasternal intercostal muscles at baseline and after each increment of sweep gas flow are reported in [Figure 2](#). The EMG activity of *Alae nasi* and parasternal muscles decreased in response to the 4 l/min increase in sweep gas flow (p=0.0002 and p=0.0001, respectively).

Correlations between dyspnea and drive

Correlations between EMG activity of *Alea nasi* and parasternal muscles and dyspnea-VAS, A1, SQ, and A2 scores of the MDP are reported in [Figure 3](#). There were significant positive correlations between EMG activity of *Alea nasi* and dyspnea-VAS (Rho 0.410 95% confidence interval [CI] 0.195 – 0.587, $p = 0.0003$) and SQ (Rho 0.333, 95% CI 0.093 – 0.536, $p=0.006$) and between EMG activity of parasternal muscle and dyspnea-VAS (Rho 0.411, 95% CI 0.205 – 0.582, $p=0.0001$) and SQ (Rho 0.232, 95% CI -0.004 – 0.444, $p=0.048$). There were no significant correlations between EMG activity of *Alea nasi* and A1 (Rho 0.085 95% [CI] -0.166 – 0.325, $p = 0.495$) and A2 (Rho 0.144, 95% CI -0.106 – 0.378, $p=0.244$) and between EMG activity of parasternal muscle and A1 (Rho 0.179, 95% CI -0.060 – 0.398, $p=0.199$) and A2 (Rho 0.232, 95% CI -0.040 – 0.416, $p=0.092$).

Correlations between dyspnea, PaCO₂, and sweep gas flow

Correlations between dyspnea-VAS, PaCO₂ and sweep gas flow are reported in [Figure S1 in the Online Supplement](#). There was a significant negative correlation between sweep gas flow and dyspnea-VAS (Rho -0.679 95% [CI] -0.778 – -0.532, $p < 0.0001$). There were no significant correlation between PaCO₂ and dyspnea-VAS (Rho 0.136, 95% CI -0.097 – 0.356, $p=0.236$) and between PaCO₂ and sweep gas flow (Rho 0.028, 95% CI -0.204 – 0.257, $p = 0.808$). There was a significant negative correlation between sweep gas flow and the A1 affective component of the MDP, but there was no correlation between A1 and PaCO₂ (see [Figure S2 in the Online Supplement](#)).

Discussion

This study opens a window on dyspnea in patients undergoing vaECMO, by illustrating that these patients can report severe dyspnea. It also shows that, increasing the sweep gas flow relieves dyspnea with a parallel reduction in respiratory drive. Although an increasing sweep gas flow had an effect on all the components of dyspnea, this effect was more marked for the

sensory component of dyspnea than for the affective component. In addition, there was a significant correlation between the respiratory drive and the sensory component of dyspnea, while there was no correlation between the respiratory drive and the emotional and affective components of dyspnea.

The recognition of dyspnea as a major ICU stressor is recent ²⁴. Dyspnea is indeed frequent in ICU patients. It is reported by 35% to 50% of intubated patients ^{1,2} and 55% of patients treated with non-invasive ventilation ³. When present, dyspnea is severe as it reaches a median value of 50 on a dyspnea-VAS from 0 to 100. In ICU patients, dyspnea has disastrous consequences. First, it is an immediate cause of suffering as dyspnea causes fear, the fear of dying. In addition, dyspnea is strongly associated with anxiety ^{1,24}. Second, dyspnea comes first among the dark recollections of the ICU stay ²⁵. Dyspnea is also associated with occurrence of post-traumatic stress disorder syndrome ². For all these reasons, dyspnea should be looked for and fought in critically ill patients. To date, information on dyspnea in ECMO patients is scarce despite being the most severe patients in ICU with therefore a high likelihood of dyspnea. Indeed, the interplay between the respiratory muscles and the brain is complexified by the ECMO device, which allows to mediate the PaCO₂ and possibly modify the patient's breathing pattern. Dyspnea occurs when the respiratory drive increases ¹⁰, as a consequence of respiratory system load capacity imbalance. In patients with heart failure, dyspnea is likely to happen, due to cardiogenic pulmonary edema, which increases respiratory loading ⁹ and stimulates interstitial J receptors ²⁶ that belong to the C-fibers family that has been implicated in dyspnea pathophysiology ²⁷. In the present study, when dyspnea was present in vaECMO patients, its intensity was high (50 mm on a VAS from zero to 100 mm). A similar level of pain would trigger an immediate therapeutic response ²⁸.

Various approaches may be used to mitigate dyspnea, like treating its cause when possible, ventilator settings adjustments in mechanically ventilated patients ^{1,29} or the

administration of opioids³⁰. Here, we provide a very simple tool to relieve dyspnea in ECMO patients. In ECMO patients, changing sweep gas flow and subsequently CO₂ removal through the membrane can modulate respiratory drive since CO₂ is a powerful stimulus of respiratory drive. In a previous report on patients with an acute respiratory distress syndrome, increasing veno-venous ECMO sweep gas flow decreased the respiratory drive and effort¹⁷. In patients with hypercapnic severe exacerbation of COPD treated with low-flow extracorporeal CO₂ removal, reducing sweep gas flow was associated with an increase in respiratory drive¹⁶. Unfortunately, the intensity of dyspnea was not measured in these two studies.

Our study is seemingly the first to show that increasing gas sweep flow can reduce dyspnea in vaECMO patients. The relationships between hypercapnia, ventilatory drive, and dyspnea are well established^{13,14,31}. The first hypothesis that comes to mind to account for our results is that increasing gas sweep flow reduced PaCO₂, hence respiratory drive, hence dyspnea. This was the case for the first step of the sweep flow increase (Table 2) after which PaCO₂ significantly decreased, but this was not true not for the following steps, during which PaCO₂ remained stable. In addition to PaCO₂, the alveolar partial pressure in CO₂ (PACO₂) has been shown, in animal studies, to influence respiratory drive through the stimulation of vagally mediated CO₂ sensitive pulmonary C-fibers^{32,33}. During vaECMO, PaCO₂ by nature becomes uncoupled from PACO₂: one possible explanation for a decreasing respiratory drive in response to an increased gas flow sweep in spite of a stable PaCO₂ would be a decreased PACO₂ resulting from the ECMO-related removal of CO₂ stores^{34,35}. From a very practical point of view, it provides a simple, non pharmacological tool to control an awful syndrome with its relief considered by some authors a basic human right^{6,36}.

One of the most recent and significant developments in the field of the pathophysiology of dyspnea is the recognition of its multidimensional aspect³⁷⁻³⁹. On the one hand, there is a sensory component that is related to the nature of the perception. On the other hand, dyspnea

has an affective component that describes the unpleasantness of dyspnea. Physiologically, the emotional and affective components of dyspnea proceed from the cognitive-affective processing of the sensation ³⁹. Our study shows that increase in sweep gas flow through the membrane allowing modulation of CO₂ removal was associated with a higher decrease in the sensory component of dyspnea than in the affective component. CO₂ being a major stimulus of respiratory drive, our results suggest that the respiratory drive is the main determinant of the sensory component of dyspnea, but not of the emotional and affective component of dyspnea. This is reinforced by the fact that, in our study, the respiratory drive as assessed by the electromyographic activity of *Alae nasi* and parasternal intercostal muscles was significantly correlated with the sensory component of dyspnea, but not with the emotional and affective components of dyspnea.

The main strength of our study is the demonstration of the efficacy of a simple and risk-free modulation of a vaECMO parameter to relieve dyspnea. This intervention via CO₂ modulation could be used in daily practice in these patients without having to introduce drug therapy like (e.g opioids) or non-invasive ventilation.

Our study has limitations. Firstly, we did not collect tidal volume from patients ventilating spontaneously, which would have provided a better understanding of the impact of CO₂ removal on ventilation. However, for ethical reason, due to the fact that these experiments were conducted soon after the announcement of a very severe heart disease with potentially disastrous consequences and worse prognosis, adding a mouthpiece for the purpose of measuring tidal volume was felt unethical. Secondly, in order to obtain a reliable and precise evaluation of dyspnea, the study was conducted in well communicating patients who could accurately self-report their symptoms. The exclusion of non-communicative patients is a selection bias. Thirdly, our study evaluated only the short-term impact of CO₂ removal on dyspnea. We do not know the impact of this short term decrease in dyspnea on the middle and

long term impact of dyspnea. Finally, in this population of young patients who were studied a few hours after the announcement of a severe heart disease requiring vaECMO, the affective component of dyspnea (fear, anxiety, anger, frustration, depression) might have been confounded by many factors than dyspnea itself. Lastly, dyspnea was not alleviated for all patients by increasing the sweep gas flow. It suggest that beyond PaCO₂, other mediators of dyspnea are involved in acute heart failure/pulmonary edema, which were not specifically studied in our study.

In conclusion, our observations show that dyspnea may be high in patients under vaECMO and that it is possible to relieve dyspnea by simply increasing the sweep gas flow. This may avoid the excessive use of non-invasive ventilation or medications. In response to an increased CO₂ clearance, it seems to alleviate the intensity of the central respiratory drive which decreases dyspnea. It indicates a stronger relationship between the respiratory drive and the sensory component of dyspnea than between the respiratory drive and the affective component of dyspnea. Future studies are needed to understand more precisely how the modulation of CO₂ affects breathing pattern modulation and to assess the long-term impact of this intervention on the consequences of dyspnea.

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Table 1. Characteristics of the study population

<i>Demographic characteristics</i>	
Gender, male, <i>n (%)</i>	13 (62)
Age, year	40 (30–55)
Body Mass Index, <i>kg/m²</i>	25 (22–27)
<i>Comorbidities</i>	
Chronic respiratory disease, <i>n (%)</i>	0
Chronic heart failure, <i>n (%)</i>	11 (52)
<i>Reason for canulation</i>	
Dilated cardiomyopathy, <i>n (%)</i>	10 (48)
Acute myocardial infarction, <i>n (%)</i>	3 (14)
Fulminant myocarditis, <i>n (%)</i>	3 (14)
Electrical storm, <i>n (%)</i>	2 (9)
Other, <i>n (%)</i>	3 (14)
<i>Severity scores</i>	
SAPS 2 at admission	29 (24–37)
SOFA at inclusion	8 (6–9)
<i>On inclusion</i>	
vaECMO-to-inclusion interval, <i>days</i>	3 (2–4.5)
Sedation on inclusion, <i>n (%)</i>	0
RASS	0 (0–0)
Dobutamine, $\mu\text{g/kg/min}$	10 (10–10)
Nasal oxygen flow, <i>L/min</i>	2 (1–2.5)
<i>Extracorporeal circulation settings</i>	
Membrane oxygen fraction, %	70 (50–95)
Rotation per minute, <i>n/min</i>	2940 (2627–4978)
Blood flow, <i>L/min</i>	2.4 (2.2–3.1)
Sweep gas flow, <i>L/min</i>	1.0 (0.5–2.0)
Position of cannulae, femoro-femoral, <i>n (%)</i>	21 (100)

vaECMO, veno-arterial extracorporeal membrane oxygenation; RASS, Richmond Agitation and Sedation Scale; SAPS, Simplified Acute Physiology Score; SOFA, Sepsis-related Organ Failure Assessment;

Data are expressed as median (interquartile range) and number (%)

Table 2. Sweep gas flow, clinical parameters and blood gases during baseline and each 2 L/min increase in sweep gas flow

	Baseline	+2 L/min	+4 L/min	+6 L/min	p
Sweep gas flow, <i>L/min</i>	1.0 (0.5–2.0)	3.0 (2.5–4.0)	5.0 (4.5–6.0) * $\$$	7.0 (6.5–8.0) * $\$$	<0.000 1
<i>Physiologic variables</i>					
Respiratory rate, <i>min⁻¹</i>	23 (21–25)	21 (18–22)	19 (16–20) *	15 (13–17) * $\$$	<0.000 1
Heart rate, <i>min⁻¹</i>	96 (88–111)	97 (88–111)	95 (88–109)	95 (87–105)	0.177
Mean arterial blood pressure, <i>mmHg</i>	78 (72–91)	78 (73–90)	82 (73–91)	81 (72–90)	0.666
<i>Blood gases</i>					
pH	7.51 (7.48–7.54)	7.52 (7.50–7.58)	7.54 (7.50–7.60)	7.51 (7.47–7.56)	0.051
PaO ₂ , <i>mmHg</i>	85 (66–123)	99 (72–109)	90 (71–110)	88 (66–104)	0.112
PaCO ₂ , <i>mmHg</i>	37 (31–40)	33 (28–38)	32 (29–37) *	34 (31–39)	0.004
SaO ₂ , %	98 (95–99)	98 (95–99)	98 (96–99)	98 (96–99)	0.235
HCO ₃ ⁻ , <i>mmol/L</i>	28 (25–32)	28 (25–32)	27 (25–32)	28 (25–32)	0.008
Lactate, <i>mmol/L</i>	1.2 (0.8–1.5)	1.2 (0.8–1.5)	1.2 (0.8–1.5)	1.2 (0.8–1.5)	0.112

Data are expressed as median (interquartile range)

* p <0.05 compared to the Baseline condition, \$ p <0.05 compared to the +2 L/min condition,

£ p <0.05 compared to the +4 L/min condition

Table 3. Dyspnea visual analog scale (Dyspnea-VAS) and the affective (A1), sensory (QS) and emotional (A2) dimensions of the French version of the Multidimensional Dyspnea Profile questionnaire at baseline and after each 2 L/min increase in sweep gas flow

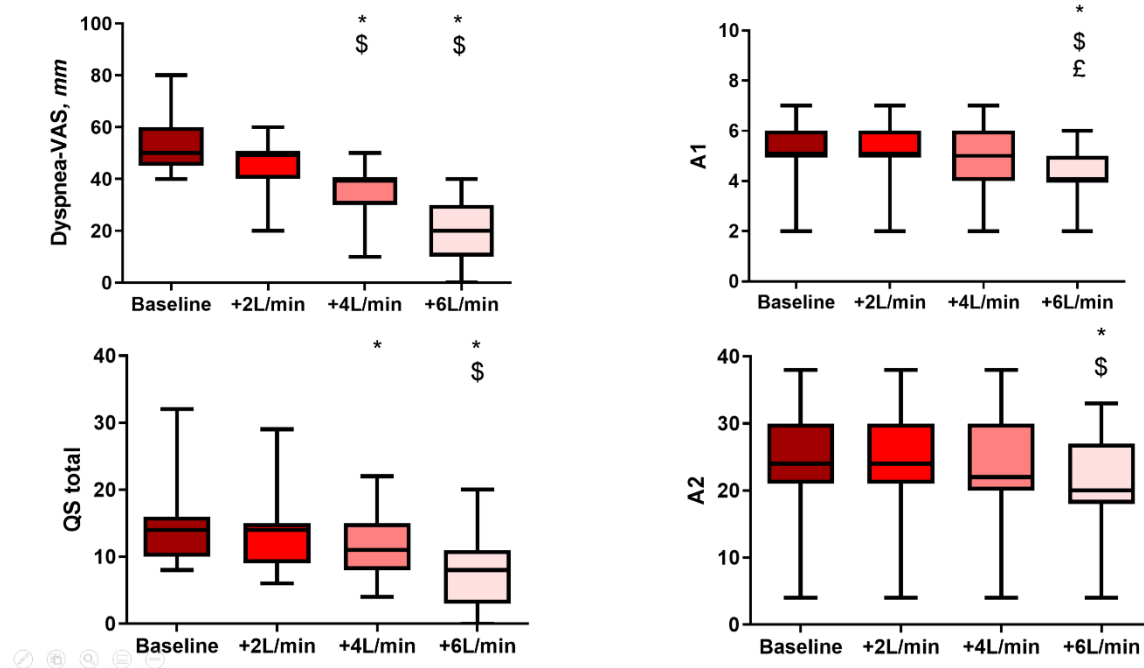
	Baseline	+2 L/min	+4 L/min	+6 L/min	p
Dyspnea-VAS, mm	50 (45–60)	50 (40–50)	40 (30–40) *\$	20 (10–30) *\$	<0.0001
MDP A1	5 (5–6)	5 (5–6)	5 (4–6)	4 (3–5) * \$ £	<0.0001
MDP QS	14 (10–16)	14 (9–15)	11 (8–15) *	8 (3–11) *\$	<0.0001
MDP physical breathing effort	5 (4–6)	5 (4–5)	4 (3–4) *	2 (1–3) *\$	<0.0001
MDP air hunger	4 (2–6)	4 (2–5)	3 (2–4)	2 (0–3) *\$	<0.0001
MDP tightness	4 (0–5)	4 (0–5)	3 (0–4)	1 (0–2) *\$	<0.0001
MDP mental breathing effort	0 (0–4)	0 (0–4)	0 (0–3)	0 (0–2)	0.004
MDP hyperpnoea	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0.261
MDP A2	24 (21–30)	24 (21–30)	22 (20–30)	20 (18–27) *\$	<0.0001
MDP depressed	5 (4–6)	5 (4–6)	5 (4–6)	4 (4–6)	0.002
MDP anxious	5 (5–6)	5 (5–6)	5 (5–6)	5 (4–6)	0.057
MDP frustrated	5 (2–7)	5 (2–7)	5 (2–7)	4 (2–5)	0.005
MDP angry	4 (2–6)	4 (2–6)	4 (2–6)	4 (0–5)	0.048
MDP frightened	6 (4–7)	6 (4–7)	6 (4–7)	4 (3–6) *	<0.0001

Dyspnea-VAS Dyspnea Visual analogue scale; A1 Affective score; QS Sensory score; A2 Emotional score; IC-RDOS Intensive Care Respiratory Distress Observation Scale

* p <0.05 compared to the Baseline condition, \$ p <0.05 compared to the +2 L/min condition,

£ p <0.05 compared to the +4 L/min condition

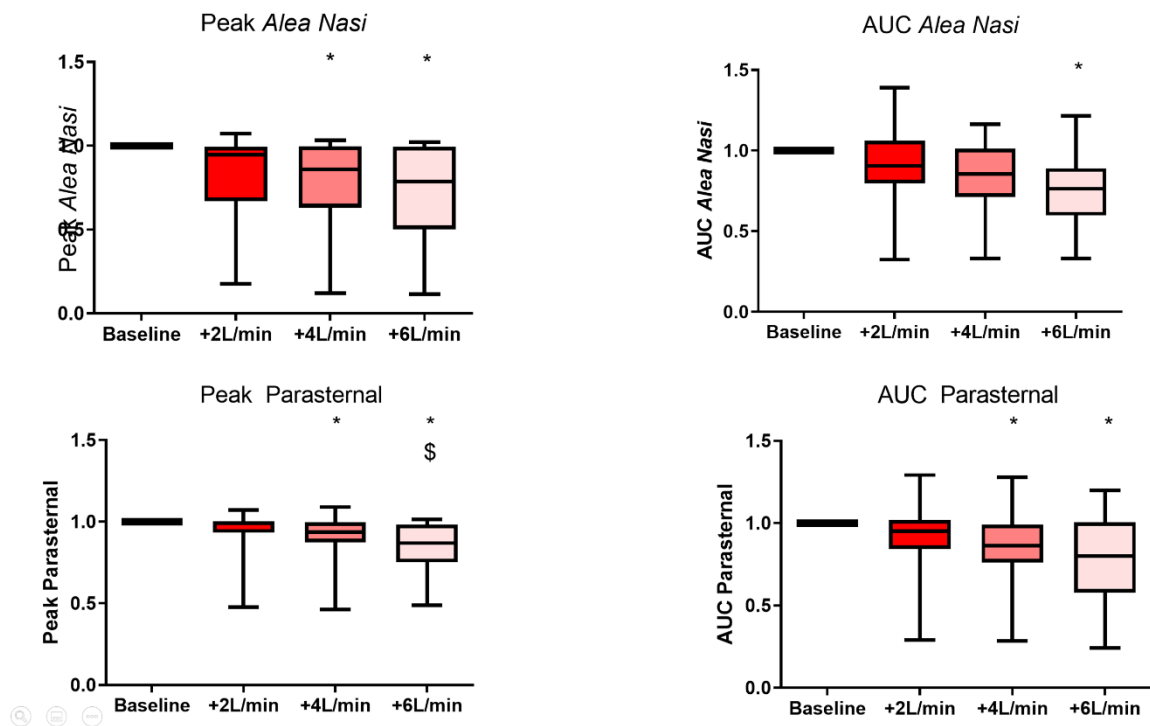
Figure 1. Dyspnea visual analog scale (Dyspnea-VAS) and the affective (A1), sensory (QS) and emotional (A2) dimensions of the French version of the Multidimensional Dyspnea Profile questionnaire at baseline and after each 2 L/min increase in sweep gas flow



Line inside the boxes median, limits of the boxes 75th and 25th percentiles of the data (interquartile range), whiskers 5th and 95th percentiles.

* p <0.05 compared to the Baseline condition, \$ p <0.05 compared to the +2 L/min condition, £ p <0.05 compared to the +4 L/min condition

Figure 2. Electromyographic (EMG) activity of the *Alae nasi* and parasternal intercostal muscles at baseline and after each 2 L/min increase in sweep gas flow

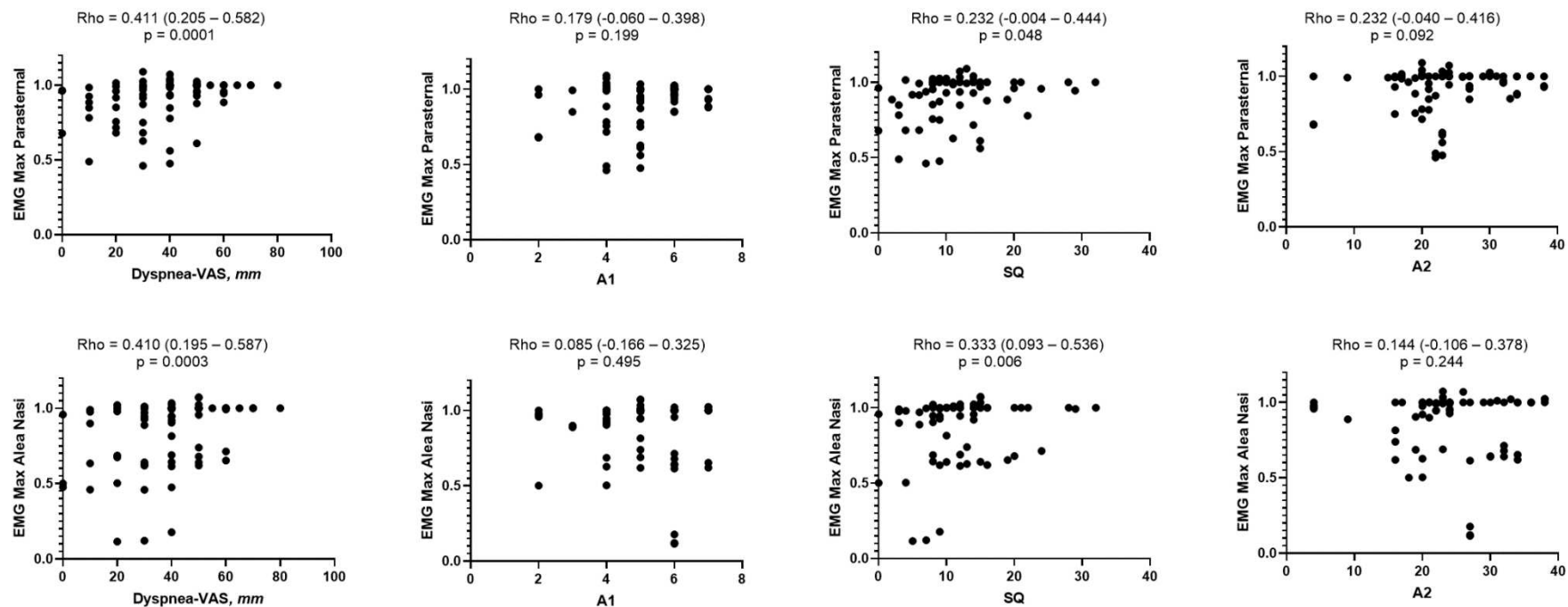


The EMG activity is described by peak EMG (EMG_{max}) and area under the curve (EMG_{AUC}) and is expressed as a proportion of the EMG activity under the baseline condition

Line inside the boxes median, *limits of the boxes* 75th and 25th percentiles of the data (interquartile range), *whiskers* 5th and 95th percentiles.

* $p < 0.05$ compared to the Baseline condition, \$ $p < 0.05$ compared to the +2 L/min condition, £ $p < 0.05$ compared to the +4 L/min condition

Figure 3. Correlation between electromyographic activity of *Alea nasi* and parasternal muscles and Dyspnea-VAS, A1, SQ and A2 scores of Multidimensional Dyspnea Profile



Dyspnea-VAS Dyspnea Visual analogue scale; A1 Affective score; QS Sensory

Increasing sweep gas flow through the membrane lung reduces dyspnea and respiratory drive in veno-arterial ECMO patients

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Online Supplemental material

Supplemental Methods 1. Detailed description of the Multidimensional Dyspnea Profile questionnaire

Figure S1. Correlation between PaCO₂, sweep gas and the dyspnea-visual analog scale (VAS)

Figure S2. Correlation between PaCO₂, Sweep gas and the A1 score of the Multidimensional Dyspnea Profile

Supplemental Data 1 : Details of Multidimensional Dyspnea Profile

The questionnaire was presented to the patient in this way.

This questionnaire is designed to help us understand how you perceive and feel about your breathing. There are no right or wrong answers. We want to know what you have to say about your breathing. First, we will ask you how uncomfortable you find your breathing. Then we will talk about the intensity (strength) of your breathing sensations.

To help you differentiate between unpleasantness and intensity, imagine that you are listening to music, for example on the radio. As the sound increases, it may be more or less unpleasant. The intensity of the sensation corresponds to the volume of the sound. As for the unpleasantness, it can appear when the sound increases or exist even if the sound is low. For example, music that you dislike will be unpleasant even if the volume is low and will become more and more unpleasant as the volume increases. On the other hand, music that you like will remain pleasant even if it is loud.

A1 scale (affect)

Use this scale to assess the unpleasantness or discomfort of your breathing sensations.

0 corresponds to "neither pleasant nor annoying"; 10 corresponds to "unbearable".

Choice QS

Rate on the following scale the intensity of the breathing sensations you experience (whether they were pleasant or unpleasant. Indeed, a sensation can, like music, be strong without being unpleasant).

0 corresponds to "I did not experience this sensation"; 10 corresponds to "the highest intensity imaginable".

- I have to work *or* make a muscular effort to breathe.

- I am short of air *or* I am suffocating *or* I feel that I need air
- I feel that my chest and lungs are tight *or* compressed.
- I have to concentrate *or* make a mental effort to breathe.
- I breathe hard.

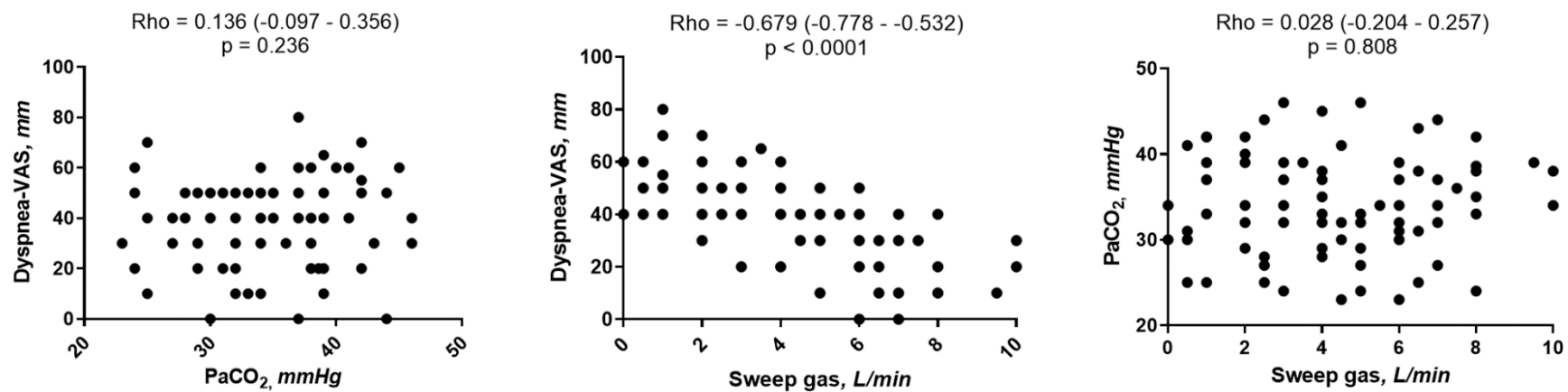
All patients were asked if they wished to add additional descriptions of their breathing sensations if necessary.

A2 scale (affect)

When you feel that you are not breathing normally, you may be experiencing emotions or "feelings. Using the following scales that I will introduce to you, please indicate how you felt about your breathing sensations - mark zero for feelings that you do not experience.

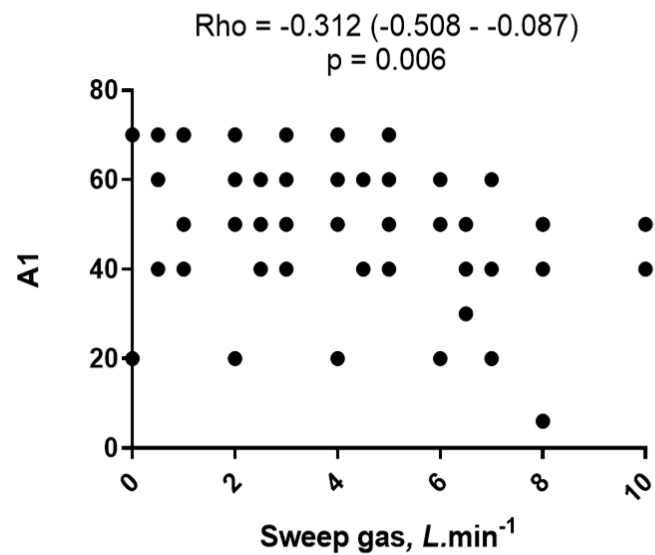
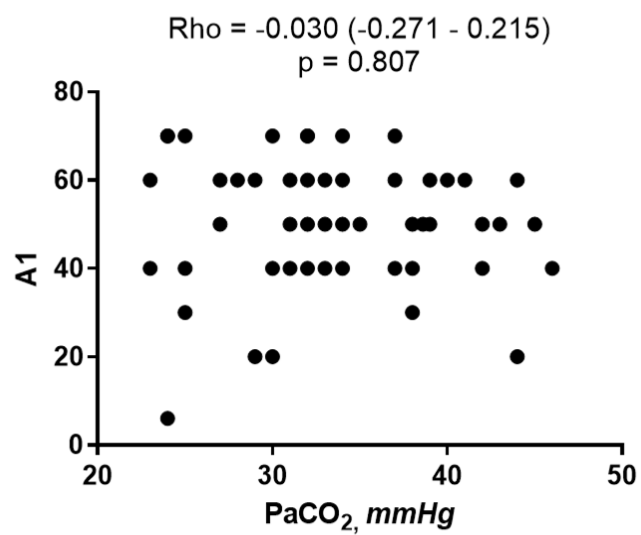
0 is "I did not experience this feeling"; 10 is "I experienced this feeling in the worst way imaginable".

Figure S1. Correlation between PaCO₂, sweep gas and the dyspnea-visual analog scale (VAS)



Dyspnea-VAS Dyspnea-Visual Analogic Scale

Figure S2. Correlation between PaCO₂, Sweep gas and the A1 affective score of the Multidimensional Dyspnea Profile



Implication respective des composantes sensorielles, émotionnelles et affectives dans le soulagement de la dyspnée chez les patients de réanimation

Résumé :

En réanimation, jusqu'à la moitié des patients sous ventilation mécanique présentent une dyspnée, tellement intense que, s'il s'agissait d'une douleur, elle impliquerait un traitement pharmacologique immédiat. Au-delà de la souffrance éprouvée, la dyspnée accroît le risque de syndrome de stress post-traumatique. Cette thèse a pour objectif d'étudier, chez des patients de réanimation, la contribution respective des composantes émotionnelles, affectives et sensorielles de la dyspnée lors d'interventions visant à soulager la dyspnée, et le lien entre ces composantes et l'intensité de la commande respiratoire centrale.

Les résultats montrent 1) que la dyspnée serait davantage liée à l'activité électromyographique des muscles inspiratoires extradiaphragmatiques qu'à celle du diaphragme, 2) que l'amélioration de l'équilibre charge-capacité par la personnalisation de la ventilation artificielle diminue la dyspnée, en diminuant la commande centrale, 3) que la stimulation du nerf trijumeau par un flux d'air vers le visage et l'écoute d'une musique relaxante diminuent toutes les composantes de la dyspnée, sans diminution notable de la commande centrale par une modulation des composantes affectives et émotionnelles. La commande centrale n'explique ainsi pas la dyspnée, puisque celle-ci diminue sans modifier notablement la commande centrale, et que la modulation des composantes émotionnelles et affectives supprime la corrélation dyspnée - commande centrale, 4) qu'augmenter l'épuration du CO₂ en augmentant le balayage dans la membrane d'ECMO diminue la dyspnée et la commande centrale. L'existence d'une corrélation significative commande centrale - composante sensorielle, sans corrélation commande centrale - composantes émotionnelles et affectives appuie le lien de causalité entre commande centrale et composante sensorielle.

Mots clés : dyspnée, neurophysiologie, soulagement, électromyographie des muscles inspiratoires, ventilation mécanique

Respective involvement of sensory, emotional, and affective components in the relief of dyspnea in resuscitation patients

Abstract :

In intensive care, up to half of the patients under mechanical ventilation present a dyspnea, so intense that if it were a pain, it would require an immediate pharmacological treatment. Beyond the immediate suffering, dyspnea increases the risk of post-traumatic stress disorder. The aim of this thesis is to study, in intensive care patients, the respective contribution of the emotional, affective, and sensory components of dyspnea during interventions aiming at relieving dyspnea, and the link between these components and the intensity of the respiratory drive.

The results show 1) dyspnea is more related to the electromyographic activity of the extradiaphragmatic inspiratory muscles than to that of the diaphragm, 2) the improvement of the load-capacity balance by the personalization of artificial ventilation decreases dyspnea, by decreasing the drive, 3) the stimulation of the trigeminal nerve by an air flow towards the face and the listening of a relaxing music decrease all the components of the dyspnea, without notable decrease of the drive by a modulation of the affective and emotional components. The drive does not explain the dyspnea since the dyspnea decreases without noticeably modifying the drive and that the modulation of the emotional and affective components suppresses the dyspnea - drive correlation, 4) increasing the CO₂ purification by increasing the sweep in the ECMO membrane decreases the dyspnea and the drive. The existence of a significant drive-sensory component correlation, without a drive-emotional and affective component correlation supports the causal link between drive and sensory component.

Keywords : dyspnea, neurophysiology, relief, electromyography of inspiratory muscles, mechanical ventilation