THÈSE POUR OBTENIR LE GRADE DE DOCTEUR DE L'UNIVERSITÉ DE MONTPELLIER

En Anesthésie-Réanimation (section 48)

École doctorale Science du Mouvement Humain (SMH)

Unité de recherche PhyMedExp - INSERM U1046 - CNRS UMR 9214
Physiologie et Médecine Expérimentale du Coeur et des Muscles

Nouveaux déterminants et outils d'évaluation innovants de la dysfonction diaphragmatique et du sevrage ventilatoire en réanimation et médecine périopératoire

Présentée par Mathieu CAPDEVILA
Le Mardi 12 Décembre 2023

Sous la direction du Pr Samir JABER
et du Pr Audrey DE JONG

Devant le jury composé de

M. le Professeur Samir JABER, PU-PH, Université de Montpellier	Directeur de thèse
Mme. la Professeur Audrey DE JONG, PU-PH, Université de Montpellier	Co-directeur de thèse
Mme. la Professeur Karine NOUETTE-GAULAIN, PU-PH, Université de Bordeaux	Rapporteur
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M. le Professeur Laurent BROCHARD, PU-PH, University of Toronto	Examinateur
M. le Professeur Pierre ALBALADEJO, PU-PH, Université Grenoble Alpes	Examinateur
M. le Professeur Stefan MATECKI, Université de Montpellier	Président de jury

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UNIVERSITÉ DE MONTPELLIER

REMERCIEMENTS :

A Monsieur le Professeur Samir JABER. Un grand merci pour ton enseignement, ton suivi, ta rigueur. Merci pour ta détermination, pour ta culture de l'excellence et de l'intégrité. "Les datas que des datas, en science on ne ment jamais". Merci pour les ambitions que tu portes à tous tes élèves. Merci pour avoir su fédérer et créer autour de toi une équipe fantastique. Merci de nous guider et de nous accompagner toujours plus loin.

A Madame la Professeur Audrey De JONG. Merci pour ton accompagnement et pour ta grande disponibilité. Merci pour tes conseils avisés et tes relectures de dernière minute. Avoir accès à ton expertise est une chance incroyable pour moi. Merci pour ta gentillesse, ta bonne humeur et pour ton flegme sans pareil.

A Madame la Professeur Karine NOUETTE-GAULAIN. Merci d'avoir accepté de juger ce travail. C'est un honneur et une joie de t'avoir dans mon jury de thèse. Tu es un véritable moteur pour la spécialité et un exemple à suivre tant sur le plan médical et scientifique que sur le plan personnel. Je ne perds pas espoir d'obtenir un jour la recette de tes fameux canelés !

A Monsieur le professeur Jean-Michel CONSTANTIN. Un grand merci d'avoir accepté d'être rapporteur de cette thèse. C'est un honneur pour moi d'avoir un des plus grands spécialistes de la ventilation mécanique dans mon jury de thèse. J'espère être à la hauteur.

A Monsieur le professeur Laurent BROCHARD. Un grand merci de me faire l'honneur d'être présent dans ce jury de thèse. Un immense merci pour votre expertise et vos conseils avisés concernant les travaux présents dans ce travail de thèse. C'est un véritable privilège pour moi de côtoyer l'un des plus grands experts mondiaux en physiologie respiratoire.

A Monsieur le Professeur Pierre ALBALADEJO. Merci d'avoir accepté de participer à ce jury de thèse. Merci pour l'intérêt porté à ce travail. C'est un grand honneur pour moi. Cette thèse finira peut-être dans la SFAR Galaxie, qui sait !

A Monsieur le Professeur Stefan MATECKI. Merci d'avoir accepté d'être présent dans ce jury de thèse. Merci pour ton enseignement depuis les bancs de la faculté de médecine. Merci pour ton accompagnement dans ce travail de thèse. Pour ta culture scientifique que tu transmets, pour toute l'énergie que tu mets à rapprocher les équipes de recherche fondamentale et de recherche clinique. Pour ta bonne humeur, ton dynamisme, ta motivation.

Un immense merci à toutes les équipes du DAR B sans qui ce travail n'aurait jamais pu voir le jour. A l'équipe de recherche, Albert et Aurélie pour leur accompagnement au quotidien et leur grande implication. Aux IDE et aux internes qui ont participés aux "gardes cochons". A tous mes co-internes de l'époque et mes co-chefs d'aujourd'hui pour votre aide, votre soutien, votre compréhension.

Merci aux copains de la KRA, les fameux SIX ! Yassir ton expertise clinique, ta motivation et ta détermination infinie. J'ai entendu dire que Yassir c'est mieux que Chat GPT, tu lui donnes un manuscrit brouillon et tu reçois en moins de 24h un New England tout écrit prêt à publication. Merci aux deux Clément, Monet et Lebibi, pour votre disponibilité, votre gentillesse et votre accompagnement à tout instant. Merci à Joris, le jeune, mon voisin tréviésois, pour tes conseils avisés en stats, pour ta bonne humeur. Merci à Ines, nouvelle venue mais déjà pleinement intégrée, pleine d'idées et motivée comme jamais.

Merci à tous les co-internes et tous les co-chefs qui ont jalonnés mon parcours, à tous les DAR. J'ai tellement appris à vos côtés.

Merci aux copains du GROUPE ! Pour votre accompagnement sans faille depuis … toujours ! Dodo j'ai enfin une vraie thèse à présenter !

Merci à toute ma famille, ma mère, mon père un exemple à suivre qui m'inspire dans ce parcours universitaire.

A Laura, pour ton soutien sans faille. Pour ton aide précieuse dans ce travail. Une formidable attachée de recherche clinique privée.

A Liam, à Charlie. Merci pour le bonheur que vous nous apportez. Je suis fier de vous.

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INTRODUCTION

La ventilation est une activité vitale dont le rôle est d'assurer les échanges gazeux entre l'extérieur et la circulation sanguine. Trois grandes fonctions sont nécessaires à la ventilation. La fonction de commande ventilatoire, responsable de l'automatisation de la ventilation, assurée par les centres nerveux respiratoire au niveau du tronc cérébral. La fonction d'échangeur gazeux, responsable des transferts d'oxygène et de dioxyde de carbone entre l'extérieur et la circulation sanguine, assurée par le poumon au niveau alvéolaire. La fonction de pompe ventilatoire, responsable des mouvements d'air entre l'extérieur et l'alvéole, assurée par les muscles respiratoires avec le diaphragme au premier plan.

La ventilation mécanique, assurée par un respirateur, est le premier support d'organe en réanimation. Elle permet d'assurer le rôle de pompe ventilatoire et d'automatisation de la ventilation en cas de sédation ou de troubles neurologiques. En cas de dysfonction diaphragmatique, fréquente en réanimation, il sera difficile de se passer du respirateur pour assurer les mouvements d'air. La dysfonction diaphragmatique est donc associée à l'échec du sevrage de la ventilation mécanique. Et c'est un cercle vicieux car la ventilation mécanique est la principale cause de dysfonction diaphragmatique.

A ce jour, la physiopathologie de la dysfonction diaphragmatique liée à l'excès d'assistance ventilatoire est bien comprise et bien documentée. L'autre versant, l'atteinte diaphragmatique liée au manque d’assistance et à l’excès d’effort inspiratoire, reste controversée et peu explorée. Il existe plusieurs outils diagnostiques pour la dysfonction diaphragmatique, mais seule la mesure post stimulation phrénique est objective et indépendante de l'activité respiratoire spontanée. Elle est complexe à mettre en place, difficilement accessible et nécessite une équipe spécialisée. Les outils plus simples utilisables au chevet du patient doivent gagner en fiabilité. Les conséquences de la dysfonction diaphragmatique sont les difficultés de sevrage ventilatoire. Au-delà de la force brute du diaphragme, les pratiques dans l’évaluation de la capacité du patient à respirer sans

assistance après extubation n’ont pas été réévaluer récemment avec les respirateurs de dernière génération, et ne sont pas forcément adaptée à tout type de pathologie.

La première partie de cette thèse est consacrée à la synthèse des connaissances sur la dysfonction diaphragmatique et son impact sur le sevrage ventilatoire. Nous verrons les bases anatomiques et physiologiques, l'épidémiologie de la dysfonction diaphragmatique, sa physiopathologie avec l'état des connaissances actuelles, les différents outils d'évaluation disponibles à ce jour, ainsi que les perspectives thérapeutiques dans le contexte. Nous verrons l'impact de la dysfonction diaphragmatique sur le sevrage ventilatoire et les pratiques actuelles sur l'évaluation des aptitudes à la ventilation spontanée.

La seconde partie de cette thèse est consacrée aux travaux réalisés selon 3 axes. Dans un premier temps nous décrirons l'impact de la ventilation assistée inadaptée, de la sous assistance et des dyssynchronies, sur la fonction et la structure du diaphragme. Dans un second temps nous présenterons deux outils diagnostics innovants permettant l'évaluation de la fonction diaphragmatique au chevet du patient, et l'estimation de la qualité structurelle du diaphragme de façon simple et non invasive. Enfin dans un troisième temps nous réévaluerons les pratiques des épreuves de ventilation spontanée avec les conditions de réanimation moderne et de médecine périopératoire, et nous explorerons les différences qui peuvent exister selon la pathologie du patient.

Cette thèse a bénéficié du soutien de l'Université de Montpellier et du soutien de la Société Française d'Anesthésie et de Réanimation.

SYNTHESE DES CONNAISSANCES

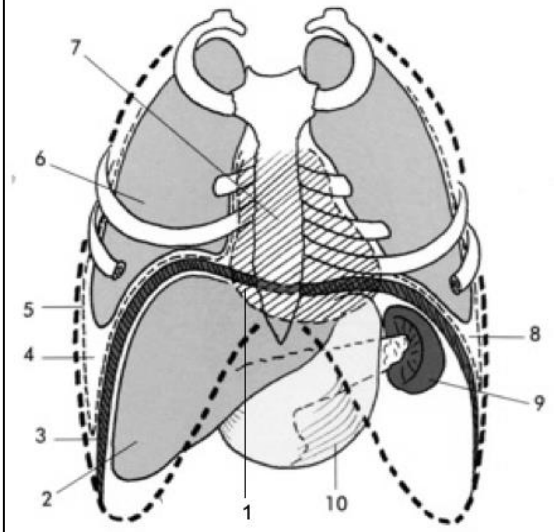
I. Dysfonction diaphragmatique

1. Anatomie et physiologie du muscle diaphragmatique

Le diaphragme est un muscle en forme de dôme, séparant le thorax de l'abdomen (**figure 1**). Il comporte une structure centrale tendineuse, et des fibres musculaires qui rayonnent à partir de ce centre. Il s'insère en avant au niveau du processus xiphoïde, et en arrière sur les vertèbres lombaires et le psoas. En latéralité il s'insère sur la paroi thoracique au niveau des six dernières côtes (K6 à K12) constituant la zone d'apposition, région d'intérêt pour l'échographie diaphragmatique (1). C'est un muscle strié squelettique, constitué de fibres musculaires de type 1 en majorité (contraction lente, oxydatives, peu fatigables), associé à des fibres de type 2 (rapide, glycolytiques, fatigables) (2). Il fonctionne 24h sur 24, avec des contractions rythmiques involontaires, mais il permet aussi la contraction volontaire. La coupole diaphragmatique s'abaisse à la contraction, entrainant une pression négative dans le thorax et donc un mouvement d'air dans le poumon. Comme tous les muscles striés squelettiques, il existe une relation force-longueur pour les fibres musculaires diaphragmatiques. Ainsi lorsque la configuration spatiale n'est pas optimale (muscle aplati par distension thoracique du patient emphysémateux, ou distension abdominale en post opératoire), on retrouve une altération de la force diaphragmatique (3).

Le diaphragme est innervé par les nerfs phréniques droit et gauche, innervation motrice exclusive, qui naissent au niveau du plexus cervical (C3 à C5). Dans la région cervicale ces nerfs cheminent entre le muscle sterno-cleïdo mastoïdien et le scalène antérieur, puis descendent dans le médiastin pour finir par de nombreuses ramifications sur la coupole diaphragmatique.

Figure 1 : Rapports anatomiques du diaphragme



1- Diaphragme (dôme)
2- Foie
3- Diaphragme (zone d'apposition)
4- Cul de sac pleural
5- Plèvre
6- Poumon
7- Cœur
8- Cul de sac pleural
9- Rate
10- Estomac

2. Epidémiologie de la dysfonction diaphragmatique

La dysfonction diaphragmatique est définie par une inadéquation entre la force produite par le muscle diaphragmatique et les besoins ventilatoires du patient. Elle est fréquente en réanimation. Selon le contexte, la population étudiée et l'outil diagnostic utilisé, l'incidence peut varier de 29% à 80% (4-10). Son apparition peut être précoce dès l'initiation de la ventilation mécanique (5), dès 24 heures après admission en réanimation (4). Elle est plus fréquente chez le patient présentant une neuromyopathie de réanimation, après 48h de ventilation mécanique (9). Elle a un impact fort sur le sevrage ventilatoire avec plus de 50% d'échec après deux essais (10). Le devenir du patient est affecté avec une majoration des échecs de sevrage (7, 11-13), un risque accru de réadmission en réanimation après une sortie de l'ordre de 30% (14) et une augmentation de la mortalité en réanimation et à long terme (4, 5, 9).

3. Physiopathologie de la dysfonction diaphragmatique

La ventilation mécanique est un des principaux facteurs contribuant à la dysfonction du diaphragme. Il existe 4 grands mécanismes responsables de la dysfonction diaphragmatique

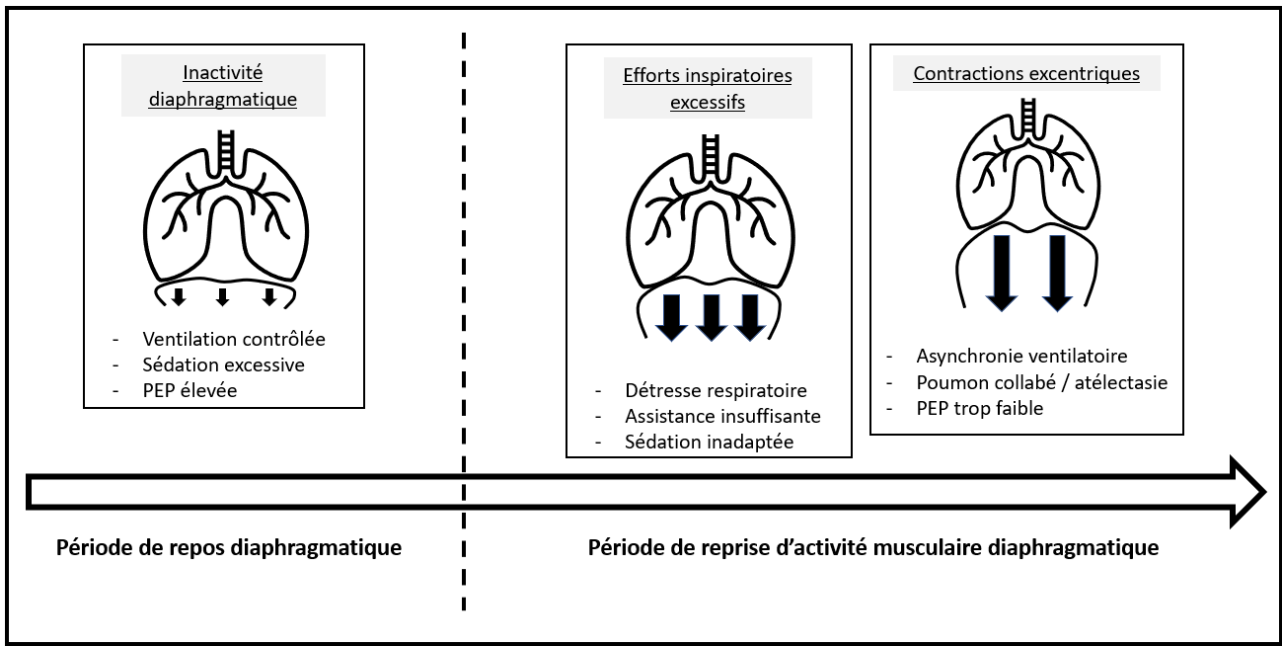
induite par la ventilation mécanique (15-19). L'inactivité diaphragmatique par excès d'assistance et de sédation. L'effort excessif par manque d'assistance et de sédation cette fois-ci. Les contractions excentriques (contraction sur un diaphragme en cours d'étirement), qui surviennent essentiellement lors de certaines asynchronies ventilatoires. Enfin, une entité plus complexe qui devrait mieux se définir dans les années à venir : le myotrauma expiratoire qui regroupe l'atrophie longitudinale due à la pression expiratoire positive (PEP) (20) et les dyssynchronies liées à l'activité excessive des muscles expiratoires.

Il existe deux grandes périodes à risque pour la dysfonction diaphragmatique (figure 2) :

- La période de mise au repos du diaphragme favorisant l'atrophie secondaire à l'inactivité ou l'hypoactivité musculaire.

- La période de reprise d'activité diaphragmatique amenant le risque d'hyperactivité musculaire (travail respiratoire excessif) et d'activité contrariée (contractions excentriques).

Figure 2 : Deux périodes à risque et trois mécanismes de dysfonction diaphragmatique induite par la ventilation mécanique



L’atrophie des fibres musculaires diaphragmatique est directement associée à une diminution de la contractilité in vitro et in vivo (12, 21). Le degré d'atrophie est lui corrélé à la durée de ventilation contrôlé, soit la durée de mise au repos forcé du diaphragme. A l'inverse la ventilation assistée a un effet protecteur (22). A cela se rajoute l'atrophie dite longitudinale, liée à la PEP élevée (20). Le diaphragme est aplati, un phénomène de retrait des sarcomères se met en place par longueur de fibres devenu inutile. Par la suite lorsque le diaphragme retrouve sa position initiale à la baisse de PEP et reprise de l'activité spontanée, il y a un étirement des fibres et une altération des caractéristiques tension-longueur du muscle.

L'effort inspiratoire excessif, ou charge concentrique excessive, est lié à une demande respiratoire élevée, une assistance insuffisante et une sédation inadaptée. Le patient est amené à réaliser de fréquents et puissants mouvements contractiles du diaphragme pourvoyeurs de tension importante nocive. Encore plus délétère, les contractions excentriques sont des contractions profondes à partir d'un diaphragme étiré favorisé par un poumon collabé, par les atélectasies et par une PEP faible. Les asynchronies type efforts inefficaces, reverse triggering (23) ou short cycling entrainent ces lésions, la contraction du diaphragme s'effectuant lors de la phase expiratoire (poumon affaissé, diaphragme étiré). Ces deux mécanismes "traumatiques" entrainent une désorganisation des myofibrilles et un infiltrat inflammatoire intra-musculaire. Chez certains patients l'œdème lésionnel peut être trompeur, en augmentant l'épaisseur du diaphragme il laisse croire à une récupération fonctionnelle du muscle.

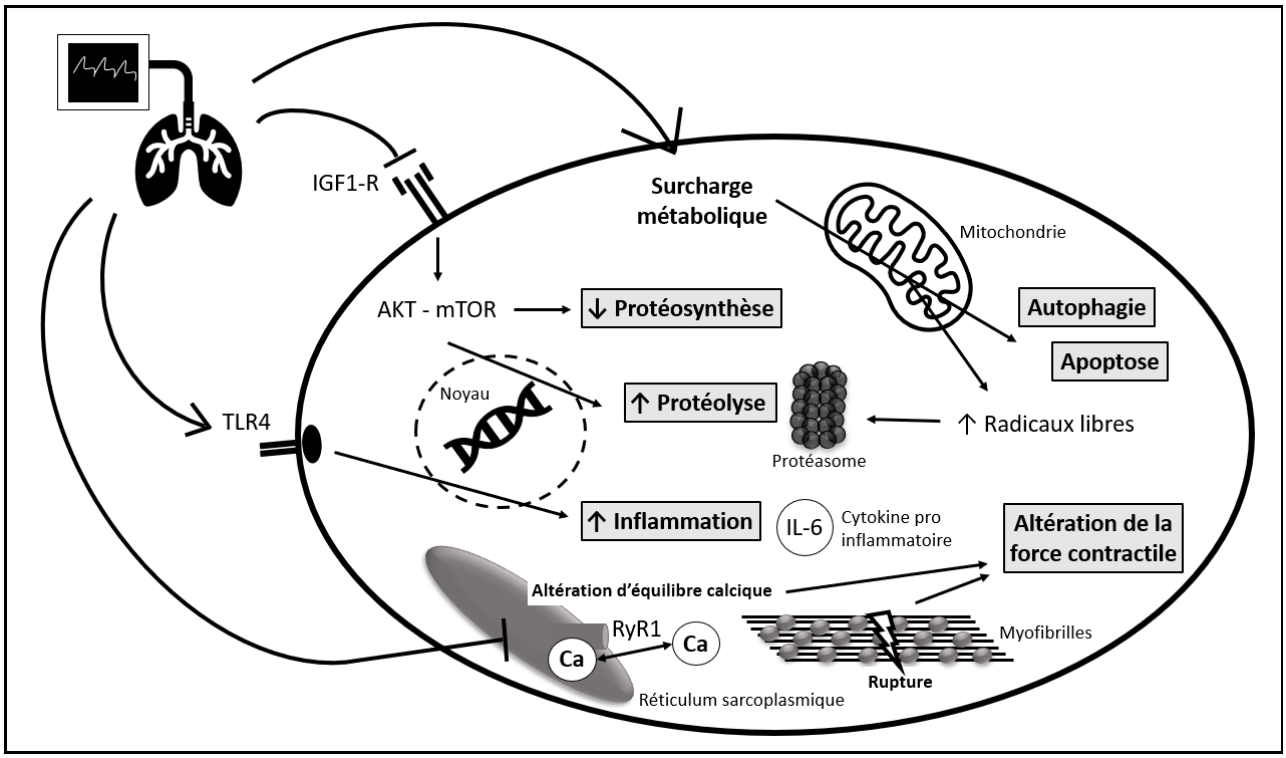
D'un point de vue cellulaire (3, 24), l'atrophie du muscle est expliquée par un remodelage en défaveur du tissu musculaire. Il a été montré une franche diminution de la protéosynthèse, par inactivation de la voie IGF-1 AKT mTOR (Insulin Growth Factor type 1, Protéine kinase B, mammalian target of rapamycin), et une accélération de la protéolyse par augmentation de l'activité protéasomique de dégradation des protéines. Autre phénomène responsable, la dysfonction mitochondriale par surcharge métabolique (déséquilibre entre apport énergétique

et utilisation de cette énergie) menant vers une autophagie mitochondriale, une surproduction de radicaux libres (qui vont participer à la protéolyse), et un phénomène d'apoptose.

La dysfonction s'explique aussi par une altération qualitative du muscle. Il a été observé une désorganisation des sarcomères avec un affinement des fibres contractiles secondaire à la protéolyse. De plus récents travaux ont aussi montré une altération du récepteur à la ryanodine (RyR1) entrainant une fuite calcique du réticulum sarcoplasmique et donc une altération de l'équilibre entre réabsorption et relargage calcique amenant une altération de la fonction contractile musculaire (25, 26).

Quant à l'inflammation cellulaire observée, elle est provoquée par l'activation de la voie TLR4 (Toll-like receptor 4), qui amène une production de cytokines pro inflammatoires.

Figure 3 : Eléments cellulaires de la dysfonction diaphragmatique induite par la ventilation mécanique. (IGF1-R : Insulin Growth Factor type 1 ; AKT : Protéine kinase B ; mTOR : mammalian target of rapamycin ; TLR4 : Toll-like receptor 4 ; RyR1 : récepteur à la ryanodine 1 ; IL-6 : Interleukine 6).



De nombreuses autres causes de dysfonction diaphragmatique existent dans le contexte de la réanimation et de la médecine péri opératoire (3, 27):

- Atteinte centrale : AVC, Trauma, pathologie inflammatoire
- Atteinte du nerf phrénique : trauma, section/étirement chirurgicale, compression, pathologie inflammatoire
- Atteinte de la jonction neuromusculaire : myasthénie, botulisme, syndrome paranéoplasique, intoxications
- Atteinte musculaire directe : sepsis (ischémie, cytopathie, inflammation), état de choc (hypoperfusion), dénutrition, hypercapnie sévère (l'hypercapnie modérée aurait un effet protecteur), hypophosphorémie (déficit en ATP), traitements (curares, corticoïdes, sédation, amines)
- Atteinte pariétale : thoracique (volet costal), abdominal (trauma, chirurgie)

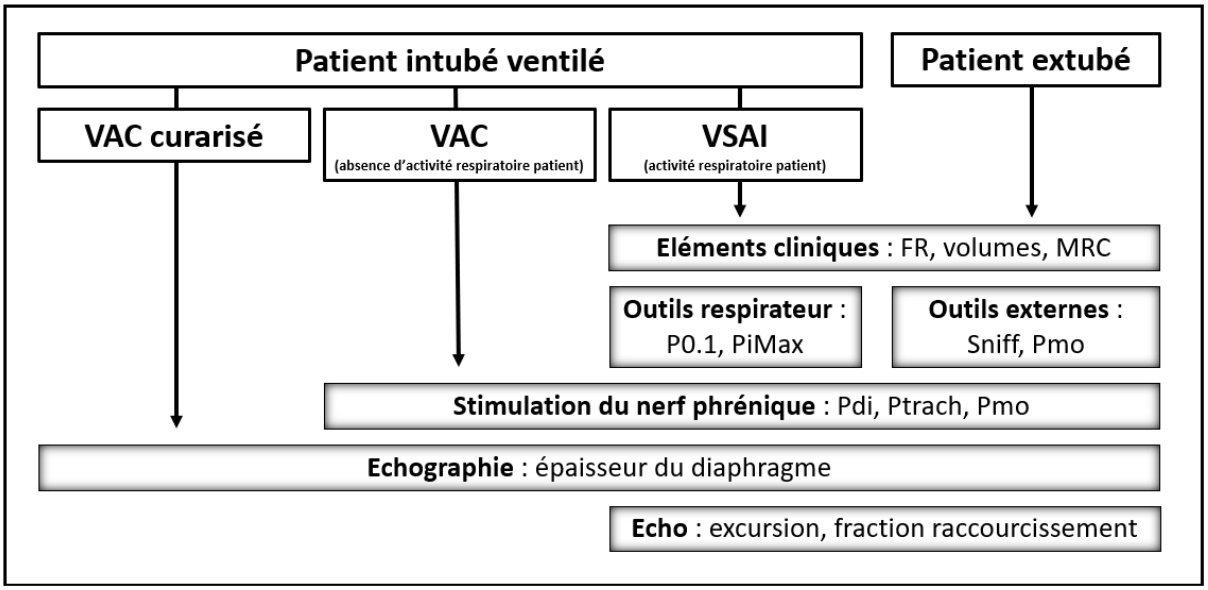
4. Outils d'évaluation de la fonction diaphragmatique

Il existe aujourd'hui une multitude d'outils nous permettant d'évaluer la fonction ventilatoire et diaphragmatique de nos patients, qu'ils soient intubés ventilés ou non, sous ventilation contrôlée ou assistée, qu'ils soient ou pas curarisés (figure 4). Le tableau 1 résume les principaux outils avec les valeurs seuils pour le diagnostic de dysfonction diaphragmatique.

Les premiers signes de la dysfonction diaphragmatique sont cliniques (1). Un patient avec une faiblesse diaphragmatique va devoir utiliser ses muscles accessoires lors de l'inspiration, il y aura donc un tirage sus-claviculaire et/ou une contraction des muscles intercostaux. De plus le diaphragme ne se contractant pas, il sera "aspiré" par la pression négative intrathoracique entrainée par les muscles accessoires, et l'abdomen également (au lieu d'être gonflé chez un sujet sain). Ce dernier se regonfle en fin d'inspiration une fois les poumons remplis, et plus encore en cas d'expiration forcée du fait de la participation des muscles abdominaux. On assiste donc à une respiration paradoxale appelée aussi balancement thoraco-abdominal (28). Le principal muscle respiratoire étant non fonctionnel, une respiration

superficielle et rapide va être observée. Aussi appelée rapid shallow breathing, elle est définie par un rapport fréquence respiratoire / volume courant > 100 c/min/mL. Chez un patient intubé ventilé avec assistance, la dysfonction diaphragmatique peut être démasquée lors d'une épreuve de ventilation spontanée par apparition de ces symptômes cliniques de faiblesse musculaire. Un autre élément clinique d'importance est la faiblesse musculaire généralisée du patient. Bien qu'il ne soit pas été démontré de franche corrélation entre la force diaphragmatique et le Medical Research Council (MRC) score (7, 9), échelle de force musculaire globale, ce dernier témoigne néanmoins d'une hospitalisation en réanimation lourde et prolongée. C'est donc un signal d'alerte.

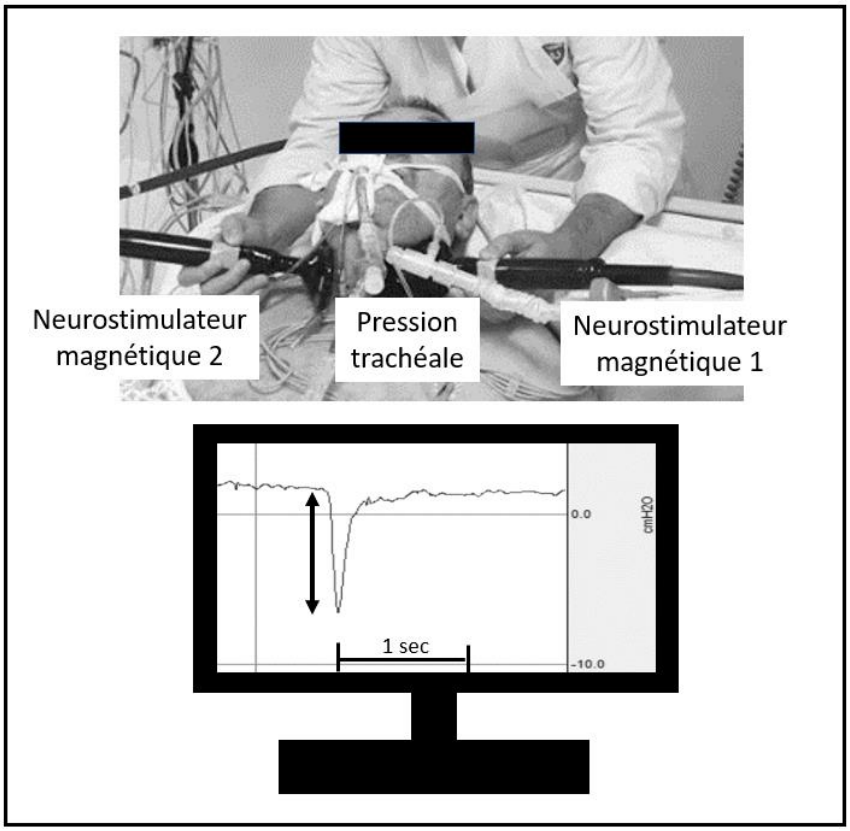
Figure 4 : Outils diagnostics de la dysfonction diaphragmatique à utiliser en fonction de l'état du patient. (VAC : ventilation assistée contrôlée ; VSAI : ventilation spontanée avec aide inspiratoire ; FR : fréquence respiratoire ; MRC score : Medical Research Council score ; P 0,1 : pression négative enregistrée lors des 100 premières millisecondes de l'inspiration ; PiMax : pression inspiratoire maximale ; Sniff : Sniff test ; Pmo : pression inspiratoire avec interface buccale ; Pdi : pression transdiaphragmatique ; Ptrach : pression trachéale)



Encore aujourd'hui considéré comme le Gold Standard (29), l'évaluation de la force diaphragmatique après stimulation du nerf phrénique a beaucoup évoluée.

La stimulation électrique (avec repère anatomique), complexe et douloureuse, a été peu à peu délaissée au profit de la stimulation magnétique. Le stimulateur est chargé à 100%, les deux palettes sont placées au niveau cervical de part et d'autre, proches des nerfs phréniques (30). Le circuit ventilatoire est clampé en fin d'expiration, et on déclenche la stimulation qui va entrainer une contraction rapide du diaphragme (un hoquet). On va alors mesurer la pression négative entrainée par cette contraction (figure 5). La stimulation magnétique est non douloureuse, ne demande pas de participation du patient, et peut se réaliser chez le patient extubé comme intubé, en VSAI ou en VAC, mais non curarisé.

Figure 5 : Evaluation de la force diaphragmatique avec stimulation phrénique magnétique



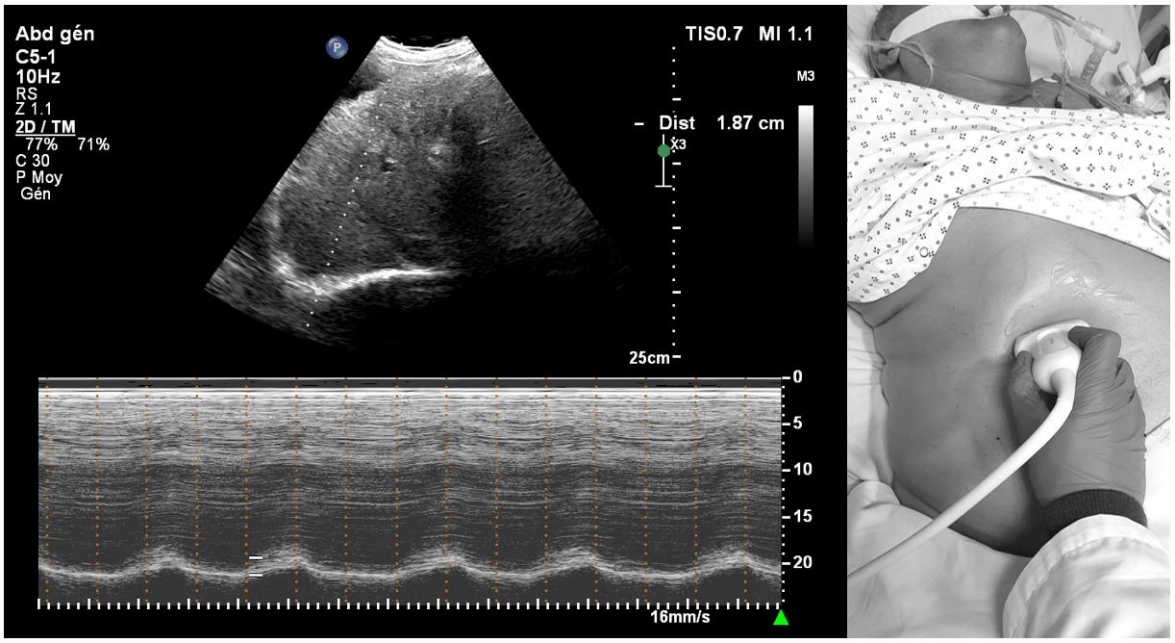
L'outil de mesure a lui aussi évolué. Initialement la pression transdiaphragmatique (Pdi) était utilisée, précise et spécifique au diaphragme elle demande toutefois le placement de deux sondes manométriques au niveau de l'œsophage et de l'estomac. Puis la sonde œsophagienne seule a été évaluée, et finalement la pression au niveau du circuit de ventilation, dite pression trachéale (Ptrach). Le circuit clampé, toutes les pressions, de l'alvéole au respirateur, s'égalisent. La pression négative entrainée par la contraction diaphragmatique est donc recueillie aisément, à n'importe quel endroit du circuit. On définit l'existence d'une dysfonction diaphragmatique lorsqu'après stimulation, on obtient en valeur absolue une Ptrach < 11 cmH2O (29). Chez le patient extubé on peut utiliser une interface buccale, on mesure alors la pression buccale (Pmo). On peut aussi mesurer l'activité électrique du diaphragme après stimulation à l'aide d'un électromyogramme (EMG). L'absence de réponse signifiant une lésion majeure du nerf phrénique, une diminution d'amplitude de la réponse motrice une atteinte axonale, l'allongement de la latence une altération myélinique.

L'échographie ayant connu un essor dans nos services de réanimation et de médecine péri opératoire, son utilisation pour l'évaluation de la dysfonction diaphragmatique a donc émergé (27). C'est un outil accessible, avec un apprentissage rapide. Elle ne nécessite pas de participation volontaire du patient, mais ce dernier doit avoir une activité respiratoire spontanée (en dehors de la mesure de l'épaisseur du diaphragme). Il existe deux approches échographiques du diaphragme.

Tout d'abord l'approche sous costale (figure 6). Une sonde abdominale ou cardiaque (5MHz) est placée en sous costal, au niveau de la ligne médio-claviculaire, avec un axe parallèle à la dernière côte. Il faut chercher une ligne hyperéchogène convexe qui se rapproche de la sonde à l'inspiration et qui constitue le diaphragme. Le sommet de cette ligne doit être si possible au centre de l'écran. Cette approche est plus facilement réalisable à droite avec la fenêtre acoustique hépatique. Une fois en place on lance le mode TM et on enregistre les mouvements du diaphragme. Le déplacement de cette ligne dans le temps représente la

course ou l'excursion diaphragmatique (6, 31), <10 mm elle est en faveur d'une dysfonction diaphragmatique.

Figure 6 : Echographie diaphragmatique, approche sous costale. Image TM à gauche, placement de la sonde à droite

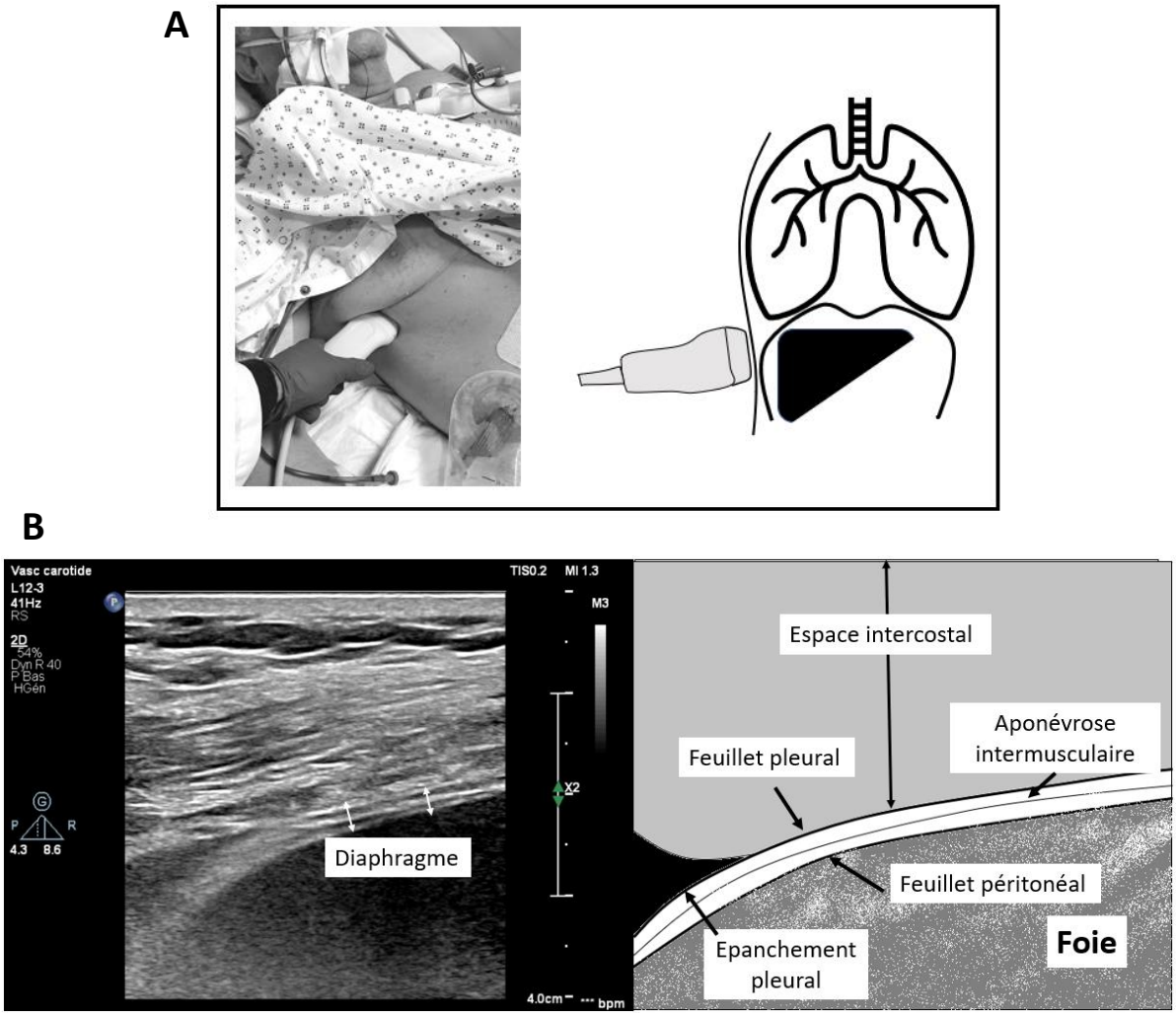


L'approche intercostale ensuite (figure 7). Il faut placer une sonde linéaire (10-15MHz) entre le 8ème et le 11ème espace intercostal, sur la ligne médio axillaire, dans l'axe cranio-caudal. C'est la zone d'apposition du diaphragme sur la paroi thoracique. On voit apparaitre deux lignes hyperéchogènes avec une couche hypo échogène au centre, au-dessus du foie à droite et de la rate à gauche. Elles constituent le diaphragme avec un feuillet pleural, un feuillet péritonéal. La qualité de l'image est assurée si l'on visualise en plus une 3ème ligne hyperéchogène coupant la couche musculaire hypoéchogène en son centre correspondant à l'aponévrose entre les deux chefs du diaphragme.

Par cette approche, nous pouvons mesurer l'épaisseur du diaphragme en fin d'expiration (32). Seule mesure réalisable quelle que soit la condition ventilatoire du patient, même curarisé. Une épaisseur < 2 mm est admis pour considérer une atrophie. L'intérêt de cette

mesure simple est probablement dans la possibilité de suivi de la trophicité du diaphragme chez les patients à risque.

Figure 7 : Echographie diaphragmatique, approche intercostale. (A) Placement de la sonde à gauche, repère anatomique à droite. (B) Image mode 2D à gauche, schématisé à droite

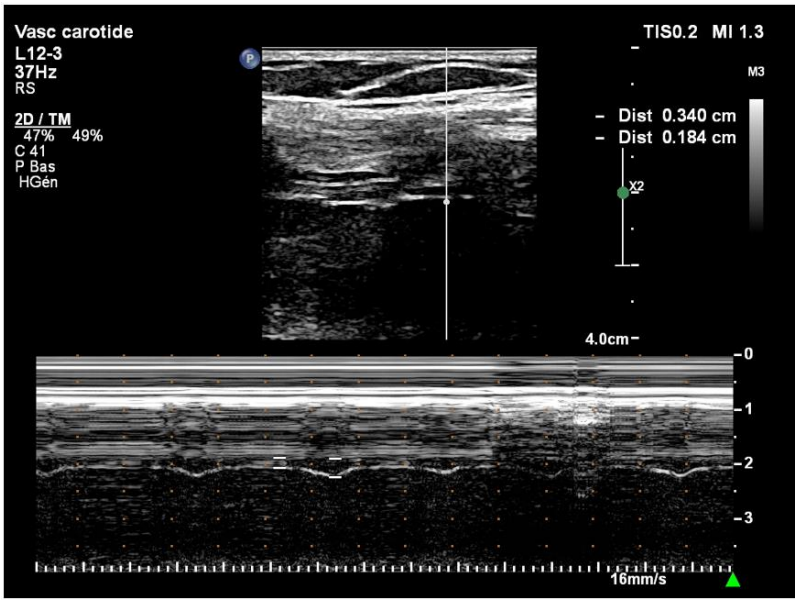


En utilisant le mode TM, nous pouvons également réaliser la fraction de raccourcissement du diaphragme (figure 8) (6), résultat de la formule :

$$\frac{\text{épaisseur à l'inspiration} - \text{épaisseur à l'expiration}}{\text{épaisseur à l'expiration}} \times 100$$

Une fraction de raccourcissement inférieure à 20% est en faveur d'une dysfonction diaphragmatique. Là encore, le suivi de l’évolution la fraction de raccourcissement, par exemple pour une aide au sevrage est intéressant.

Figure 8 : Echographie diaphragmatique, approche intercostale, image mode TM



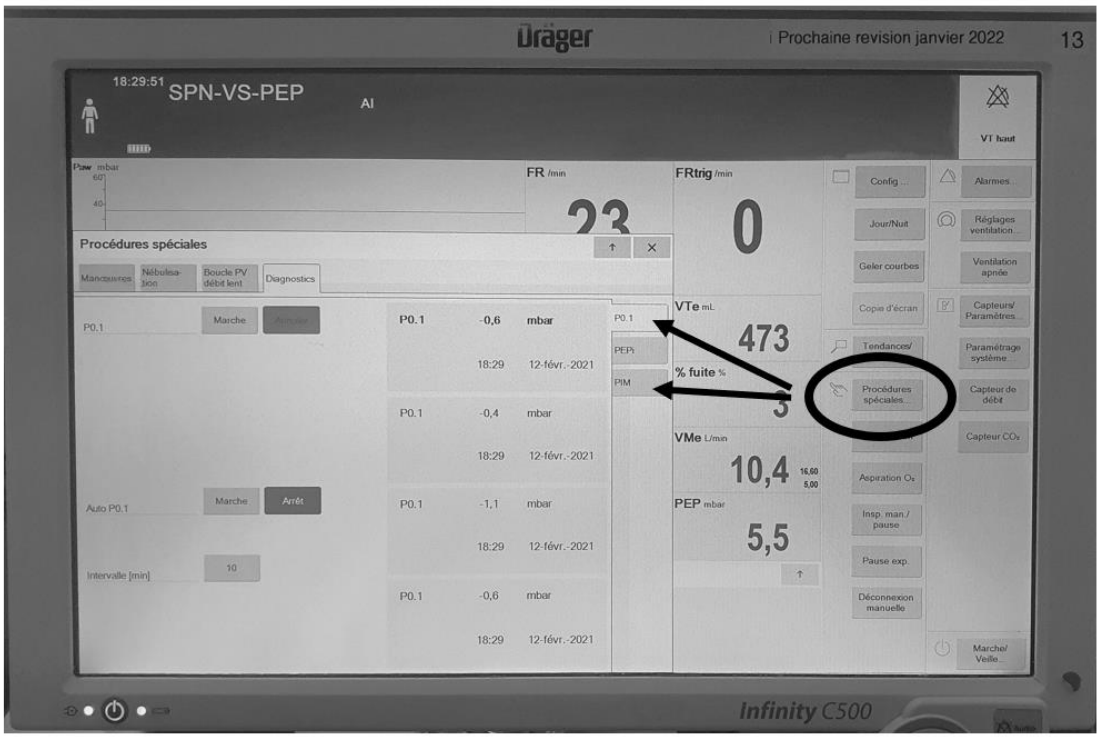
Les respirateurs modernes possèdent des outils d'évaluation intégrés permettant d'évaluer la force ventilatoire des patients, que l'on trouve souvent dans un onglet "procédures spéciales" (figure 9).

Le premier étant la pression inspiratoire maximale (33), appelée PiMax, PIM ou NIF (Negative inspiratory force). Elle nécessite la pleine coopération du patient. Lorsque le bouton est enclenché, une fois atteint la fin d'expiration, les valves inspiratoires et expiratoires se bloquent. A ce moment-là on demande au patient une inspiration maximale. La machine va alors enregistrer la pression négative maximale entrainée par cette inspiration forcée. Une pression <36 cmH2O en valeur absolue est associée à une difficulté de sevrage ventilatoire.

Il faut toutefois savoir qu'avec cette méthode on ne mesure pas uniquement la force du diaphragme, mais celle de tous les muscles inspiratoires.

Un second outil est la mesure de la P 0.1, pression négative enregistrée lors des 100 premières millisecondes de l'inspiration. C'est surtout le reflet de la commande ventilatoire. Une valeur haute signifie une forte demande ventilatoire (détresse respiratoire aigüe), mais une valeur basse peut être un signe de dysfonction neuromusculaire.

Figure 9 : Ecran d'un respirateur avec outils diagnostics intégrés



Il est possible d'évaluer la force diaphragmatique chez le patient extubé. Cela demande sa pleine coopération. On peut utiliser une interface buccale, puis demander une pression inspiratoire maximale, en télé expiration, avec l'aide plus ou moins d'une valve unidirectionnelle (méthode de Marini). On peut sinon utiliser une interface nasale, demander au patient de se boucher l'autre narine et d'inspirer le plus fort possible (Sniff test). Dans les deux cas une valeur > 70 cmH2O en valeur absolue sera considérée comme normale (sujets sains).

Tableau 1 : seuils diagnostics à retenir, en valeur absolue. (FR : fréquence respiratoire ; Vt : volume courant ; MRC score : Medical Research Council score ; PiMax : pression inspiratoire maximale ; NIF : negative inspiratory force ; Ptrach : pression tracheale)

Outil de mesure	Norme	Dysfonction - Impact clinique
FR / Vt	NA	> 100 c/min/mL
MRC score	60	< 48
Pimax - NIF	> 70 cmH2O	< 36 cmH2O
Ptrach après stimulation	> 20 cmH2O	< 11 cmH2O
Echo : épaisseur	> 3 mm	< 2 mm
Echo : fraction raccourcissement	> 30 %	< 20 %
Echo : excursion	> 20 mm	< 10 mm

5. Pistes thérapeutiques pour la dysfonction diaphragmatique

Il n'existe pas aujourd'hui de traitement spécifique validé de la dysfonction diaphragmatique associée à la réanimation et à la médecine péri opératoire (3, 27). La prise en charge est surtout préventive.

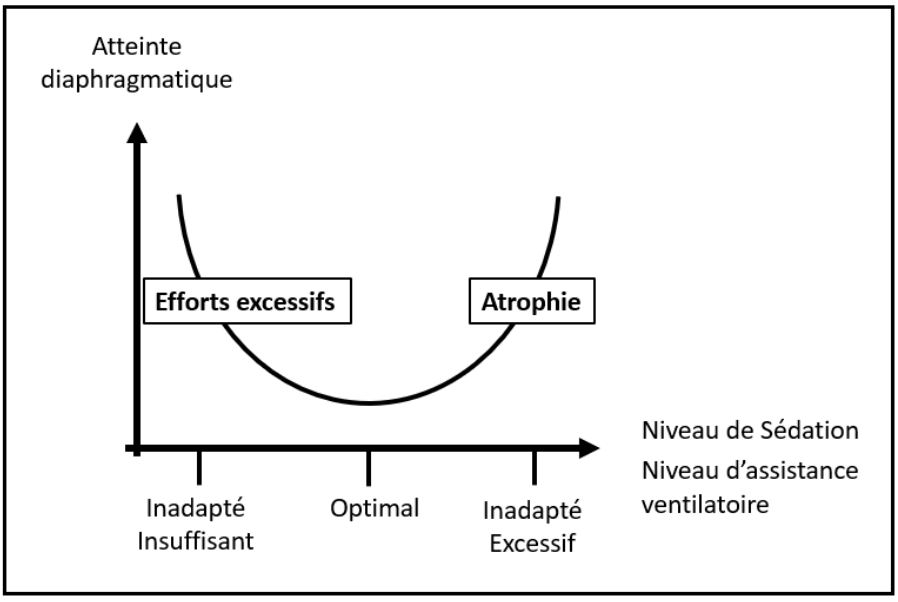
Tout d'abord sur le plan ventilatoire. Il faut privilégier dès que possible les modes assistés (22, 32), afin de permettre une activité spontanée du muscle diaphragmatique. Concernant le niveau d'aide inspiratoire, il faut le régler de façon optimale (17). Il ne faut pas sur assister le patient car le faible effort (pour le trigger) n'est pas suffisant pour protéger de l'atrophie. Il ne faut pas non plus sous assister, au risque d'entrainer des efforts inspiratoires excessifs puis l'épuisement. Il ne faut pas se contenter de regarder les volumes que prend le patient avec un niveau d'aide donné, car même sans assistance un patient peut recruter un volume d'air important avec un effort maximal, mais pour combien de temps. Il faut rester clinique et regarder sa mécanique ventilatoire, s'assurer qu'il n'y ait pas de polypnée, pas de tirage. Concernant la PEP, il faut faire attention aux niveaux élevés, qui entrainent une atrophie longitudinale.

Par ailleurs il ne faut pas laisser pour compte le réglage du trigger inspiratoire et du cyclage expiratoire. Ils sont essentiels pour éviter les asynchronies ventilatoires. Un trigger à 1 ou 2 L/min et un cyclage expiratoire à 25% du débit expiratoire sont en général de bons niveaux pour assurer une ventilation synchrone.

Il est intéressant de noter que les modes ventilatoires automatisés ou autres modes « intelligents » n'ont jamais fait la preuve de leur supériorité par rapport aux modes conventionnels.

Le second point essentiel dans la prévention de la dysfonction diaphragmatique est la gestion de la sédation. En effet le couple sédation / ventilation est indissociable. Au même titre que pour l'assistance ventilatoire, le niveau d'analgésie et de sédation doit être optimisé (figure 10). Beaucoup de progrès ont été fait ces dernières années sur la sédation excessive (34). La réévaluation et l'arrêt quotidien des sédations font partie de nos pratiques. Maintenant il faut faire attention aux excès inverses et garder des niveaux adaptés pour limiter les phénomènes d'agitation, d'efforts excessifs et d'asynchronie ventilatoire.

Figure 10 : schématisation du niveau optimal de sédation et d'assistance ventilatoire



Après avoir passé la phase aigüe, après avoir traité la pathologie initiale, la seconde étape sera la rééducation et la réhabilitation musculaire. Concernant le diaphragme, elle commence

par une évaluation quotidienne de la nécessité de ventilation mécanique invasive. La réalisation d'épreuves de ventilation spontanée (EVS) répétées, en plus de servir d'outil d'évaluation du sevrage ventilatoire, peuvent être une méthode de réentrainement simple à mettre en œuvre. Il existe aussi aujourd'hui des outils spécifiques de réhabilitation des muscles inspiratoires, avec des résistances progressivement croissantes, qui ont fait leurs preuves notamment dans le succès du sevrage et la durée de ventilation mécanique (35).

Au vu des enjeux majeurs, la recherche concernant les pistes thérapeutiques de la dysfonction diaphragmatique est en ébullition constante. Tout un pan concerne la stimulation phrénique thérapeutique (36-39). Une stimulation phrénique quotidienne avec l'aide d'une voie veineuse centrale intégrant des électrodes de stimulation a montré une amélioration de la force ventilatoire, sans toutefois d'impact sur le pronostic et le sevrage ventilatoire des patients (37).

Concernant les pistes pharmacologiques, de nombreux traitements ont été évalué sans succès démontré chez l'homme. Les antioxydants n-acétylcystéine (40), la vitamine E, la théophylline (41). Les anti-inflammatoires spécifiques (Tocilizumab), les inhibiteurs de la protéolyse (42). L'optimisation de la contractilité avec le Levosimendan (43, 44), ou autres traitements spécifiques avec action sur la myosine, la troponine, le récepteur à la ryanodine. Des essais thérapeutiques sont en cours concernant un traitement stabilisateur du récepteur à la ryanodine.

II. Sevrage ventilatoire

1. Liens avec la dysfonction diaphragmatique

La ventilation mécanique, l'assistance ventilatoire, est le premier support d'organe en réanimation (45). Contrairement à ce qu'on pourrait penser, elle ne remplace ou n'assiste pas les poumons (échangeur gazeux) mais les muscles respiratoires (pompe ventilatoire), et donc le diaphragme au premier plan. En cas de trouble neurologique ou de sédation profonde, on pourrait étendre son rôle vers un remplacement des centres nerveux de commande

ventilatoire (automatisation de la respiration). Une fonction qui pourrait être obtenue par une stimulation phrénique.

Une fois passée la phase aigüe, un processus de sevrage de la ventilation mécanique se met en place, qui peut être plus ou moins long en fonction de la pathologie et de la durée de ventilation mécanique. La tentative de sevrage peut aussi malheureusement se solder par un échec. Dans une cohorte prospective internationale de patients de réanimation (46), seuls 65% des patients sont sevrés du respirateur à J90 dont 16% en passant par une trachéotomie. 28% sont décédés dans les 90 jours et 4% ont été transférés avant sevrage. Le sevrage ventilatoire est un enjeu majeur pour le pronostic de nos patients, et le diaphragme joue un rôle central pour atteindre cet objectif. La dysfonction diaphragmatique est associée au prolongement et à l'échec du sevrage ventilatoire (4, 5, 9, 10). En dehors de la réanimation, en périopératoire, une atteinte phrénique (nerveuse ou musculaire) est aussi associée à un sevrage prolongé (47, 48). L'atteinte diaphragmatique est aussi associée à des difficultés respiratoires à long terme (49).

2. Evaluation de l'aptitude à la ventilation spontanée

Il existe deux composantes majeures à évaluer avant l'extubation d'un patient : sa capacité à protéger ses voies aériennes et sa capacité à fournir un effort ventilatoire suffisant et prolongé. Les causes d'échec d'extubation sont d'ailleurs très partagées entre ces deux entités avec dans une cohorte récente (50) 45% de réintubation liée à des problématiques de voies aériennes, 50% liée à des problématiques de pompe ventilatoire ou d'échangeur pulmonaire, 5% mixte.

Pour estimer l'intégrité fonctionnelle et structurelle des voies aériennes post extubation plusieurs critères existent (51) tels que l'état de conscience, les capacités de déglutition, la quantité de sécrétions et la fréquence d'aspiration, le test de fuite pour prévoir le risque d'œdème laryngé (52). Pour estimer la capacité du patient à maintenir un effort respiratoire spontané après extubation il faut mettre le patient en condition de ventilation spontanée en réalisant une épreuve de ventilation spontanée (EVS). L'évaluation de la force

diaphragmatique ou ventilatoire ne suffit pas, il faut savoir si le patient est en capacité de tenir cet effort dans le temps. Il existe différente façon de réaliser une EVS et les pratiques sont très hétérogènes en France et dans le monde (50, 53). On peut réaliser une épreuve avec assistance avec de l'aide inspiratoire (AI) et / ou de la PEP, si on estime que la sonde d'intubation ou le respirateur amène un effort respiratoire supplémentaire qui ne sera plus présent après extubation et qu'il faut donc compenser pour l'épreuve. On peut sinon réaliser une épreuve sans assistance en déconnectant le patient du respirateur avec une pièce en T pour maintenir un apport d'oxygène, ou en laissant le patient branché au respirateur sans aucune assistance (sans AI ni PEP). L'épreuve dure entre 30 min et 2h, et le patient sera remis en condition ventilatoire avant épreuve pendant 1h avant de l'extuber si l'épreuve est un succès (54).

Plusieurs études physiologiques ont été réalisées pour déterminer quelle EVS réplique au mieux l'effort respiratoire qui sera demandé au patient après extubation (Tableau 2).

Tableau 2 : études physiologiques sur les épreuves de ventilation spontanée

Références	Population (n patients)	Pathologie	Evaluation de l'effort après extubation	Randomisation	Respirateurs de dernière génération
Brochard et al. 1991 (55)	11	Mixte	**Yes**	No	No
Sassoon et al. 1991 (56)	10	Mixte	No	**Yes**	No
Sassoon et al. 1992 (57)	9	BPCO	No	**Yes**	No
Nathan et al. 1993 (58)	7	Mixte	**Yes**	No	No
Petros et al. 1993 (59)	8	Mixte	No	No	No
Ishaaya et al. 1995 (60)	8	Mixte	**Yes**	No	No
Patel et al. 1996 (61)	23	Mixte	No	No	No
Straus et al. 1998 (62)	14	Mixte	**Yes**	No	No
Koh et al. 2000 (63)	44	Mixte	No	**Yes**	No
Mehta et al. 2000 (64)	20	Hypoxémique	**Yes**	**Yes**	No
Kuhlen et al. 2003 (65)	12	Mixte	No	**Yes**	No
Cabello et al. 2010 (66)	14	Mixte	No	**Yes**	No
Muttini et al. 2015 (67)	18	Mixte	No	No	No
Mahul et al. 2016 (68)	17	Obese	**Yes**	**Yes**	**Yes**
Ferreira et al. 2017 (69)	20	Mixte	No	**Yes**	No
Guerin et al. 2019 (70)	20	Mixte	No	**Yes**	**Yes**

EVS = épreuve de ventilation spontanée. BPCO = bronchopneumopathie chronique obstructive.

L'étude princeps de Brochard et al. (55) montre qu'une épreuve sans assistance entraine un effort respiratoire plus important que celui demandé après extubation. Straus et al. (62) et Mahul et al. (68) retrouvent eux un effort respiratoire similaire tandis que Nathan et al. (58), Ishaaya et al. (60) et Mehta et al. (64) ne trouvent aucune EVS atteignant l'effort demandé après extubation. Ces différences peuvent s'expliquer par une hétérogénéité de pathologies, de respirateurs, d'interfaces pour évaluer l'effort respiratoire après extubation (masque facial ou embout buccal). Le diamètre de la sonde d'intubation, la présence et la quantité de sécrétions, la présence ou non d'un système d'humidification, la présence d'un œdème laryngé, sont des facteurs pouvant modifier l'effort demandé après extubation. Ces études sont majoritairement anciennes et ont inclus peu de patients (moins de 20).

3. Les patients de réanimation, tous égaux face au sevrage ventilatoire ?

En fonction de la pathologie et des antécédents, chaque patient a des spécificités ventilatoires qu'il faut prendre en compte dans une stratégie de sevrage ventilatoire. Le patient obèse a un profil restrictif avec des pressions extra alvéolaires augmentées liées au surpoids et à l'hyperpression abdominale (71). Il doit fournir des efforts plus importants que le patient non obèse, le travail respiratoire est plus important (68). De plus un effort obstructif supplémentaire peut se surajouter après extubation, lié à une élévation de la collapsibilité pharyngée sur les dépôts graisseux (72). Pour ne pas sous-estimer l'effort respiratoire demandé après extubation, une épreuve de ventilation spontanée sans assistance type T-tube ou AI 0 cmH2O PEP 0 cmH2O semble le plus adapté, et a été démontré par le travail de Mahul et al. (68). Un patient en post opératoire de chirurgie abdominale va présenter un profil similaire restrictif avec augmentation des pressions abdominales et diminution de la capacité vitale (73). Une épreuve sans assistance parait aussi appropriée. Le patient traumatisé thoracique va aussi présenter un profil restrictif, avec une diminution de compliance de la paroi thoracique (74). Il peut s'ajouter un œdème lié à l'intubation en contexte traumatique. Une épreuve sans assistance semble appropriée. Le patient neurolésé ne présente pas d'atteinte pulmonaire à proprement parlé ni de spécificité dans la mécanique ventilatoire. Il peut par contre présenter

une hypotonie laryngée, responsable d'une augmentation de l'effort respiratoire demandé après extubation. Une épreuve sans assistance semble aussi appropriée. Concernant le patient BPCO, le phénomène obstructif est au premier plan, avec une participation notable de la sonde d'intubation. En fonction du diamètre interne de la sonde, l'effort demandé au cours d'une épreuve de ventilation spontanée peut être plus élevé que celui demandé après extubation. Pour se rapprocher au mieux des conditions de post extubation, l'ajout d'une assistance pour compenser l'effort supplémentaire lié à la sonde parait licite. Dans l'étude princeps de Brochard et al., qui défend l'épreuve avec assistance, la majorité des patients étaient obstructifs (BPCO ou asthme). Chez le patient septique, il existe une forte susceptibilité à la dysfonction diaphragmatique. Il faut donc faire très attention à l'effort demandé au patient lors de la baisse des sédations et lors de l'épreuve de ventilation spontanée pour limiter les lésions de sous assistance.

PROBLEMATIQUES ET HYPOTHESES

La ventilation mécanique est un outil à double tranchant qui permet d'assurer les fonctions ventilatoires mais qui peut aussi entrainer des lésions pulmonaires et une dysfonction diaphragmatique. Après un temps de ventilation contrôlée nécessaire pour traiter une pathologie aigue, la sédation est diminuée et le respirateur est réglé pour obtenir une ventilation assistée avec mouvements respiratoires spontanés. A ce moment là survient un équilibre délicat à mettre en place entre le patient et la machine, avec des risques de sous assistance, d'effort respiratoire excessifs et de dyssynchronies. Si les connaissances sont bien établies concernant l'impact sur le diaphragme de la surassistance ventilatoire et de la ventilation contrôlée, les données concernant la sous assistance, les efforts excessifs et les dyssynchronies sont plus controversées.

Notre première hypothèse est que la ventilation assistée inadaptée avec sous assistance et dyssynchronies a un impact sur la fonction et la structure du diaphragme, et que cet impact est d'autant plus important après une période de ventilation contrôlée prolongée.

La dysfonction diaphragmatique est fréquente en réanimation, mais elle est aujourd'hui peu évaluée. Le gold standard pour le diagnostic est la stimulation phrénique magnétique associée à la mesure de la pression transdiaphragmatique, nécessitant un matériel peu disponible et une expertise technique limitant sa démocratisation. Des outils plus simples se sont développés avec leurs limites. L'évaluation échographique de mouvement et de contraction est dépendante de l'activité spontanée du malade, l'épaisseur du diaphragme peut être faussée par la qualité de ce dernier, et les mesures de pressions trachéales à la demande n'évaluent pas spécifiquement le muscle diaphragmatique.

Notre seconde hypothèse est que l'utilisation d'un outil simple et disponible de stimulation électrique, le curamètre, associée à un repérage échographique du nerf phrénique,

permettant d'obtenir une qualité diagnostique de la dysfonction diaphragmatique similaire au gold standard.

Notre troisième hypothèse est que l'utilisation de l'élastographie couplée à l'échographie permet de déterminer la qualité structurelle du muscle diaphragmatique au-delà et de son épaisseur, et que cette dernière est associée à la fonction diaphragmatique.

La dysfonction diaphragmatique est associée à des difficultés de sevrage de la ventilation mécanique. Pour estimer les capacités du patient à respirer sans assistance après extubation on peut réaliser une épreuve de ventilation spontanée. Les pratiques concernant cette épreuve sont très hétérogènes et basées sur d'anciennes études physiologiques.

Notre quatrième hypothèse est que les épreuves de ventilation spontanée sans assistance sont à privilégier pour estimer l'effort respiratoire qui sera demandé au patient après extubation.

Notre cinquième hypothèse est que l'épreuve de ventilation spontanée doit être conduite de façon adaptée à la pathologie du patient.

TRAVAUX ET RESULTATS

I/ Chapitre 1 : nouveaux déterminants de la dysfonction diaphragmatique, impact de la ventilation assistée inadaptée sur la fonction et la structure du diaphragme

1/ Etude 1 : impact de la ventilation assistée inadaptée après une ventilation contrôlée prolongée sur la fonction et la structure du diaphragme

2/ Etude 2 : impact musculaire structurel diaphragmatique de la ventilation assistée inadaptée après une ventilation contrôlée courte et prolongée

II/ Chapitre 2 : nouveaux outils d'évaluation de la fonction et de la structure du diaphragme

3/ Etude 3 : nouvel outil d'évaluation de la fonction diaphragmatique au chevet du patient avec stimulation phrénique électrique après repérage échographique

4/ Etude 4 : évaluation musculaire qualitative et structurelle avec élastographie diaphragmatique

III/ Chapitre 3 : sevrage ventilatoire, approche moderne et sevrage personnalisé

5/ Etude 5 : quelle épreuve de ventilation spontanée pour prédire l'effort respiratoire demandé après extubation pour cinq pathologies aigues

Etude 1

Impact of inadequate assisted ventilation on diaphragm function and structure

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Travail soumis à la revue Critical Care

Résumé de l'étude :

Contexte : Une ventilation assistée inadéquate après une ventilation mécanique invasive prolongée est fréquente et associée à l'échec d'extubation, à une durée de séjour prolongée et à la mortalité. L'impact direct d'une ventilation assistée inadéquate combinant sous-assistance et dyssynchronie sur la fonction et la structure du diaphragme après une ventilation mécanique invasive prolongée n'est pas connu. L'objectif de cette étude était d'évaluer l'effet d'une ventilation mécanique sous-assistée et d'une dyssynchronie après une ventilation mécanique invasive contrôlée prolongée sur la fonction et la structure du diaphragme dans un modèle porcin.

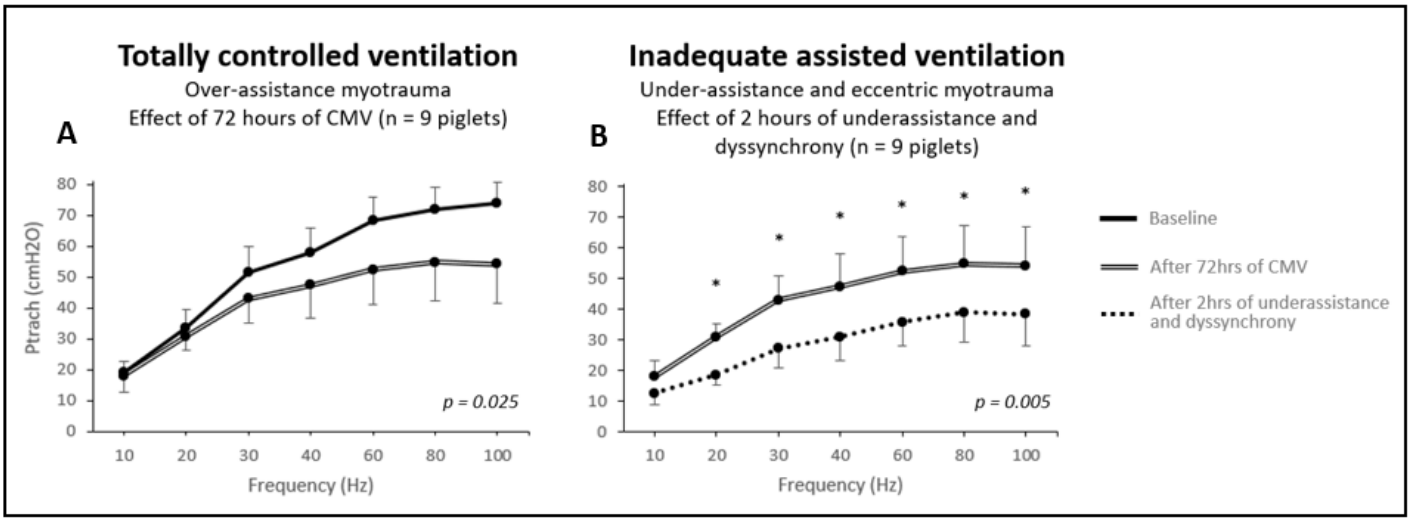
Méthodes : Dix porcelets Large-White ont été sédatés et maintenus sous ventilation mécanique invasive contrôlée pendant 72 heures suivies de 2 heures de ventilation spontanée avec sous assistance et dyssynchronie. La fonction du diaphragme (force supramaximale du diaphragme évaluée par pression trachéale négative après stimulation transveineuse du nerf phrénique) a été enregistrée à la base (début de la sédation), après 72 heures de ventilation mécanique invasive contrôlée et après 2 heures supplémentaires de ventilation assistée inadéquate. La structure du diaphragme (lésions sarcomériques) a été évaluée par microscopie électronique à partir de biopsies prélevées après 72 heures de ventilation

mécanique invasive contrôlée et après 2 heures supplémentaires de ventilation assistée inadéquate.

Résultats : La force supramaximale du diaphragme a diminué de 22 %, passant de 69,9±12,7 à 54,9±19,7 cmH2O (p=0,025) après 72 heures de ventilation mécanique invasive contrôlée attestant de la dysfonction diaphragmatique induite par la ventilation mécanique. Elle a chuté de 29% supplémentaires de 54,9±19,7 à 38,9±15,5 cmH2O (p<0,005) après 2 heures de ventilation assistée inadéquate. Les lésions sarcomériques du diaphragme représentaient 13±10% de la surface totale de la micrographie après 72 heures de ventilation mécanique invasive contrôlée, augmenté à 24±19% (p<0,001) après 2 heures de ventilation assistée inadéquate.

Conclusions : Deux heures de ventilation mécanique assistée inadéquate avec sous assistance et dyssynchronie, dans un contexte de dysfonction diaphragmatique préexistante induite par la ventilation mécanique, sont associées à une altération supplémentaire de la fonction du diaphragme et à des dommages structurels supplémentaires dans ce modèle expérimental porcin.

Figure 3: function assessment with diaphragmatic force frequency curves.



Etude 2

Longitudinal diaphragm structure assessment from in vivo biopsies after inadequate assisted ventilation in a porcine model of short versus prolonged totally controlled mechanical ventilation

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Travail soumis à la revue American Journal of Respiratory and Critical Care Medicine (research letter)

Résumé de l'étude :

Contexte : Une ventilation assistée inadéquate après une ventilation mécanique invasive prolongée est fréquente et associée à l'échec d'extubation, à une durée de séjour prolongée et à la mortalité. L'impact direct d'une ventilation assistée inadéquate combinant sous-assistance et dyssynchronie sur la structure du diaphragme n'est pas connu. L'objectif de cette étude était d'évaluer l'effet d'une ventilation assistée inadéquate après une ventilation mécanique invasive contrôlée courte versus prolongée sur la structure du diaphragme dans un modèle porcin.

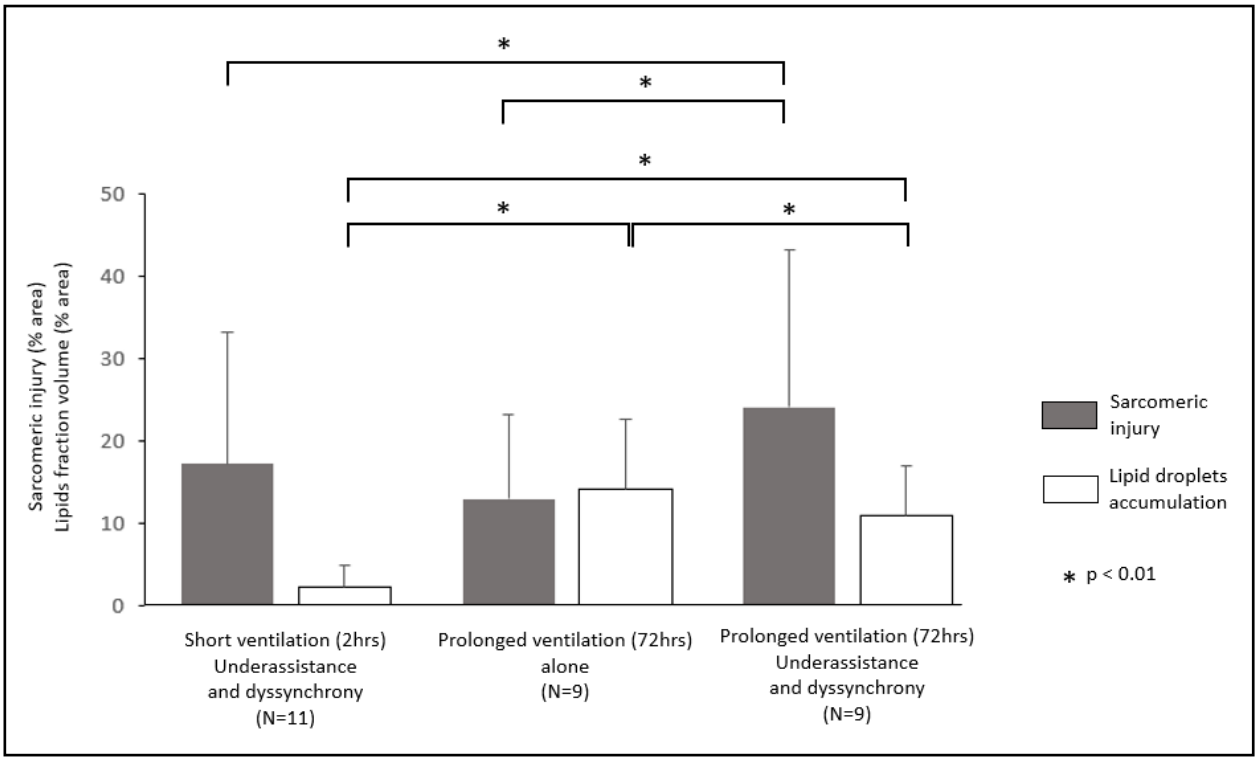
Méthodes : 22 porcelets Large-White ont été sédatés et maintenus sous ventilation mécanique invasive contrôlée pendant 2 heures pour le groupe ventilation courte (n=12) et 72 heures pour le groupe ventilation prolongée (n=10), suivies de 2 heures de ventilation spontanée avec sous assistance et dyssynchronie pour les deux groupes. La structure du diaphragme (lésions sarcomériques) et l'inclusion lipidique ont été évaluée par microscopie

électronique à partir de biopsies prélevées in vivo après 72 heures de ventilation mécanique invasive contrôlée pour le groupe ventilation prolongée et après 2 heures supplémentaires de ventilation assistée inadéquate pour les deux groupes.

Résultats : Les lésions sarcomériques du diaphragme représentaient 17±16% de la surface totale de la micrographie et les inclusions lipidiques 2.3±2.6% après 2 heures de ventilation mécanique invasive contrôlée et 2 heures de ventilation assistée inadéquate. Après 72 heures de ventilation mécanique invasive contrôlée seule, les lésions sarcomériques du diaphragme représentaient 13±10% de la surface totale et les inclusions lipidiques 14±8% (différence significative avec le groupe ventilation contrôlée courte et ventilation assistée inadéquate). La proportion de lésions sarcomériques a augmenté à 24±19% après 2 heures de ventilation assistée inadéquate supplémentaire ($p=0,03$ versus le groupe ventilation courte, et $p<0.01$ versus le groupe ventilation prolongée seule). La proportion d'inclusion lipidique a par contre diminué à 11±6.1% après 2h de ventilation assistée inadaptée ($p=0.03$ versus le groupe ventilation prolongée seule) tout en restant supérieure au groupe ventilation courte ($p<0.01$).

Conclusions : Deux heures de ventilation mécanique assistée inadéquate avec sous assistance et dyssynchronie sont associées à des dommages structurels quelle que soit la durée de ventilation qui les précèdent dans ce modèle expérimental porcin. L'inclusion lipidique est par contre plus associée à la durée de ventilation mécanique.

Figure 2: Structure assessment with percentage area of diaphragm sarcomeric injury and lipid droplets accumulation.



Etude 3

New method for bedside assessment of diaphragm function by phrenic nerve stimulation after ultrasound tracking

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Travail soumis à la revue Anesthesiology

Résumé de l'étude :

Contexte : La dysfonction diaphragmatique est fréquente en réanimation et associé à l'échec du sevrage ventilatoire et à la mortalité. Le gold standard pour le diagnostic est la pression transdiaphragmatique ou trachéale induite par la stimulation magnétique du nerf phrénique, mais l'équipement nécessaire n'est pas couramment disponible et requiert des compétences techniques spécifiques. Nous avons cherché à évaluer une nouvelle méthode appelée Sonostim pour une évaluation précoce et précise de la fonction du diaphragme au chevet du patient par stimulation électrique ciblée du nerf phrénique.

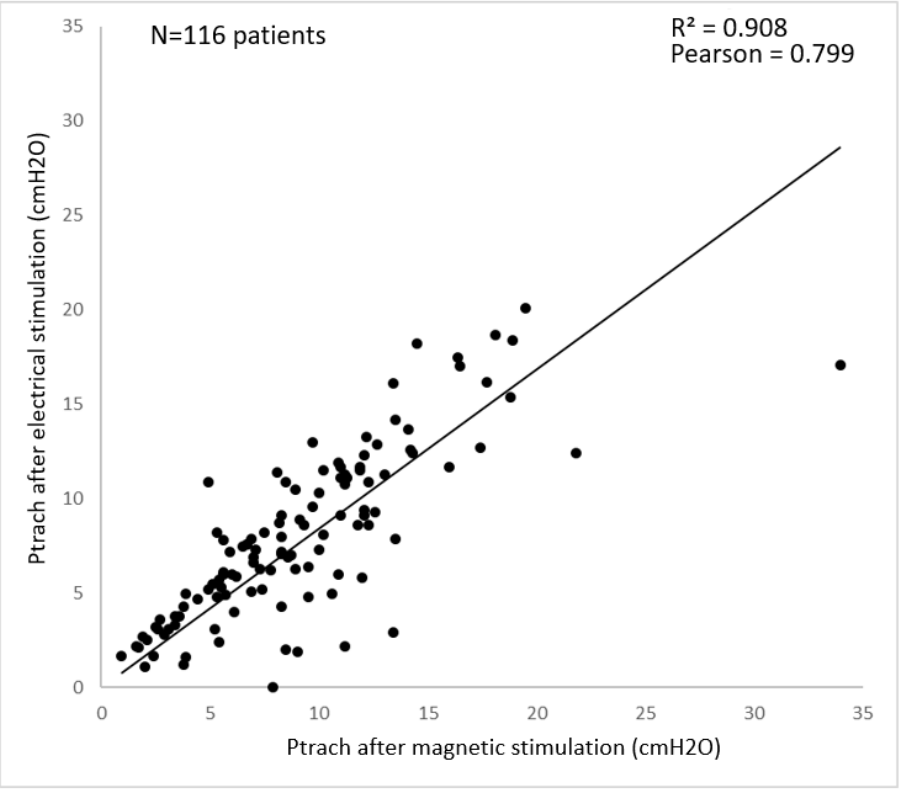
Méthodes : Dans cette étude randomisée en cross over, nous avons comparé une nouvelle méthode de stimulation électrique du nerf phrénique à l'aide d'un curamètre couplé à un ciblage échographique du nerf, à la stimulation magnétique, chez des patients adultes de réanimation sous ventilation mécanique avec un score de Richmond-Agitation-Sedation-Scale de -4 ou -5. Chaque patient a reçu les deux méthodes de stimulation, dans un ordre randomisé. Le critère de jugement principal était la pression trachéale (Ptrach) induite par la stimulation.

Résultats : Cent seize patients ont été inclus et analysés, dont 77 présentaient un une dysfonction diaphragmatique (Ptrach < 11 cmH2O) et 50 une dysfonction diaphragmatique

sévère (Ptrach < 8 cmH2O). Avec un R-carré de 0,908 (p<0,001) et une corrélation de Pearson de 0,799 (p<0,001), la méthode Sonostim a présenté une excellente corrélation avec la stimulation magnétique. Les courbes ROC ont montré une excellente performance pour le diagnostic de dysfonction diaphragmatique et de dysfonction diaphragmatique sévère avec respectivement une aire sous la courbe de 0,90 (IC95 0,83-0,97) et 0,88 (IC95 0,82-0,95). Cette performance n'était pas affectée par l'indice de masse corporelle ou la présence d'un cathéter au niveau cervical.

Conclusions : La méthode Sonostim est un outil facile à utiliser et précis pour l'évaluation de la fonction diaphragmatique au chevet du patient par stimulation du nerf phrénique après ciblage échographique.

Figure 2: Correlation between electrical stimulation using Sonostim method and magnetic stimulation.



Etude 4

Shear Wave Elastography, a New Tool for Diaphragmatic Qualitative Assessment: A Translational Study

Yassir Aarab, Aurelien Flatres, Fanny Garnier, **Mathieu Capdevila**, Fabrice Raynaud, Alain Lacampagne, David Chapeau, Kada Klouche, Pascal Etienne, Samir Jaber, Nicolas Molinari, Lucie Gamon, Stefan Matecki, and Boris Jung

Travail publié dans la revue American Journal of Respiratory and Critical Care Medicine

Résumé de l'étude :

Contexte : La ventilation mécanique prolongée est souvent associée à une diminution (atrophie connue) ou à une augmentation (lésion supposée) de l'épaisseur du diaphragme. L'élastographie par ondes de cisaillement est une technique non invasive qui mesure le module de cisaillement, un substitut de la rigidité et des propriétés mécaniques des tissus.

Objectifs : Décrire les variations du cisaillement pendant le séjour en réanimation et établir la relation avec les variations de l'épaisseur musculaire. Effectuer une caractérisation échographique complète des modifications histologiques et de la force diaphragmatique.

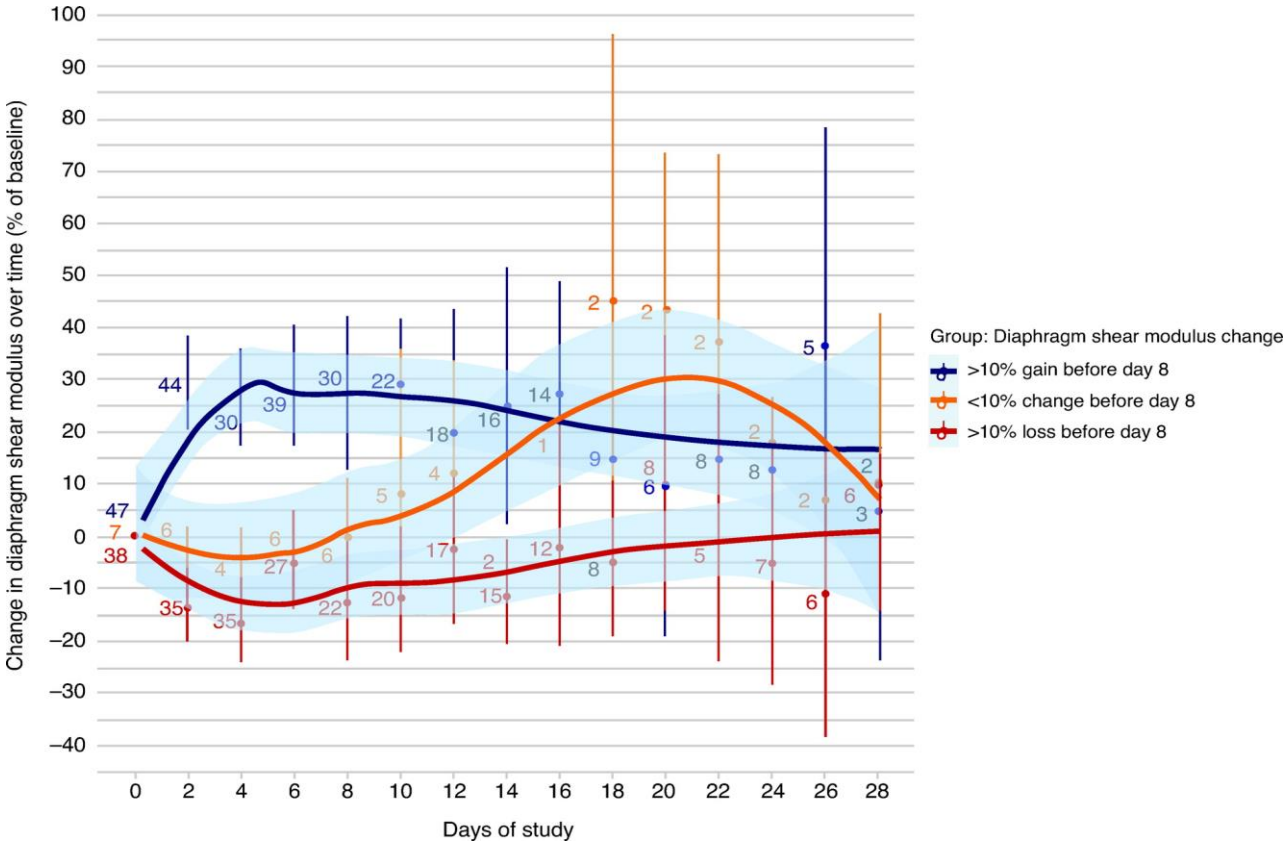
Méthodes : Étude translationnelle sur des patients critiques et des porcelets sous ventilation mécanique. Un examen échographique en série de l'épaisseur du diaphragme et du cisaillement a été effectué chez les patients et les porcelets. La pression transdiaphragmatique et les biopsies diaphragmatiques ont été prélevées chez les porcelets.

Résultats : Nous avons recruté 102 patients, dont 88 étaient sous ventilation mécanique invasive. Au départ, le cisaillement était de 14,3 ± 4,3 kPa et l'épaisseur du diaphragme en fin d'expiration était de 2,0 ± 0,5 mm. Une diminution ou une augmentation de plus de 10 % par

rapport à la valeur initiale a été signalée chez 86 % des patients pour l'épaisseur et chez 92 % des patients pour le cisaillement. Une augmentation de l'épaisseur diaphragmatique pendant le séjour a été associée à une diminution du cisaillement (β = -9,34 ± 4,41 ; P = 0,03) après analyse multivariée. Dans l'échantillon de porcelets, une diminution du cisaillement sur 3 jours de ventilation mécanique était associée à une perte de production de force, à une atrophie des fibres lentes et rapides et à une augmentation de l'inclusion lipidique.

Conclusions : L'augmentation de l'épaisseur du diaphragme chez un patient en soins critiques est associée à une diminution de la rigidité des tissus, démontrée par élastographie ultrasonore à ondes de cisaillement, ce qui correspond au développement de lésions structurelles et de faiblesses musculaires.

Figure 2: Variation in diaphragm shear modulus over time obtained in critically ill patients.



Etude 5

Which spontaneous breathing trial to predict effort to breathe after extubation according to five critical illnesses: the cross over GLOBAL WEAN study

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Editorial publié dans la revue Anesthesia, Critical Care and Pain Medicine

Protocole publié dans la revue British Medical Journal Open

Travail soumis dans la revue Lancet Respiratory Medicine

Résumé de l'étude :

Contexte : La capacité du patient de réanimation à se séparer de l'assistance ventilatoire peut être évalué par une épreuve de ventilation spontanée (EVS) qui évalue la capacité du patient à maintenir un effort respiratoire spontanée après l'extubation. Les pratiques de réalisation des EVS sont hétérogènes. L'objectif de cette étude était d'évaluer quel EVS reproduit le mieux l'effort respiratoire nécessaire au patient après extubation, en se concentrant sur cinq pathologies critiques.

Méthodes : Dans cette étude physiologique multicentrique randomisée en cross-over, des patients adultes de réanimation sous ventilation mécanique invasive depuis au moins 24 heures et prêts à être extubés ont effectué trois EVS de 15 minutes dans un ordre aléatoire : aide inspiratoire à 7 cmH2O avec une pression expiratoire positive à 0 cmH2O (AI7PEP0), AI 0 cmH2O avec PEP 0 cmH2O (AI0PEP0) et une épreuve de pièce en T. Le critère de jugement principal était le pressure time product par minute (PTPmin), reflet de l'effort inspiratoire, à

l'état de base, après chaque EVS et 20 minutes après l'extubation. Les patients ont été répartis en cinq catégories de pathologies critiques : chirurgie abdominale, neurolésés, traumatismes thoraciques, bronchopneumopathie chronique obstructive (BPCO) et divers (principalement des patients septiques).

Résultats : Cent patients ont été analysés. Le PTPmin (cmH2O.s/min, médiane et IQR) induit par les EVS sans assistance, 291 (235-347) à la fin de AI0PEP0 et 262 (198-338) à la fin de l'épreuve avec pièce en T, était similaire à celui requis après l'extubation : 256 (208-321) (pas de différence significative). L'EVS avec assistance AI7PEP0 a induit un effort inspiratoire plus faible avec 192 (127-281) (p<0-001). Chez les patients neurolésés, une seul EVS reproduit bien l'effort respiratoire demandé en post-extubation (AI0PEP0), deux EVS chez les patients ayant subi une chirurgie abdominale (AI0PEP0 et pièce en T) et chez les patients du groupe divers (PAI7PEP0 et pièce en T), les trois EVS chez les patients ayant subi un traumatisme thoracique ou une exacerbation de la BPCO.

Conclusion : Les EVS sans assistance, AI0PEP0 et l'épreuve avec pièce en T sont les plus appropriés pour reproduire l'effort respiratoire du patient après extubation.

Figure 1: Pressure time product per minute (PTPmin) at baseline, at the end of the three spontaneous breathing trials and 20 minutes after extubation for overall analyzed patients.

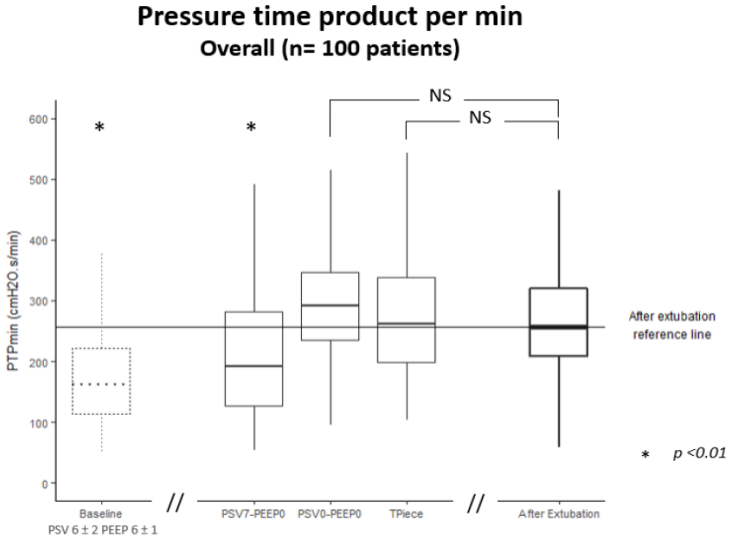
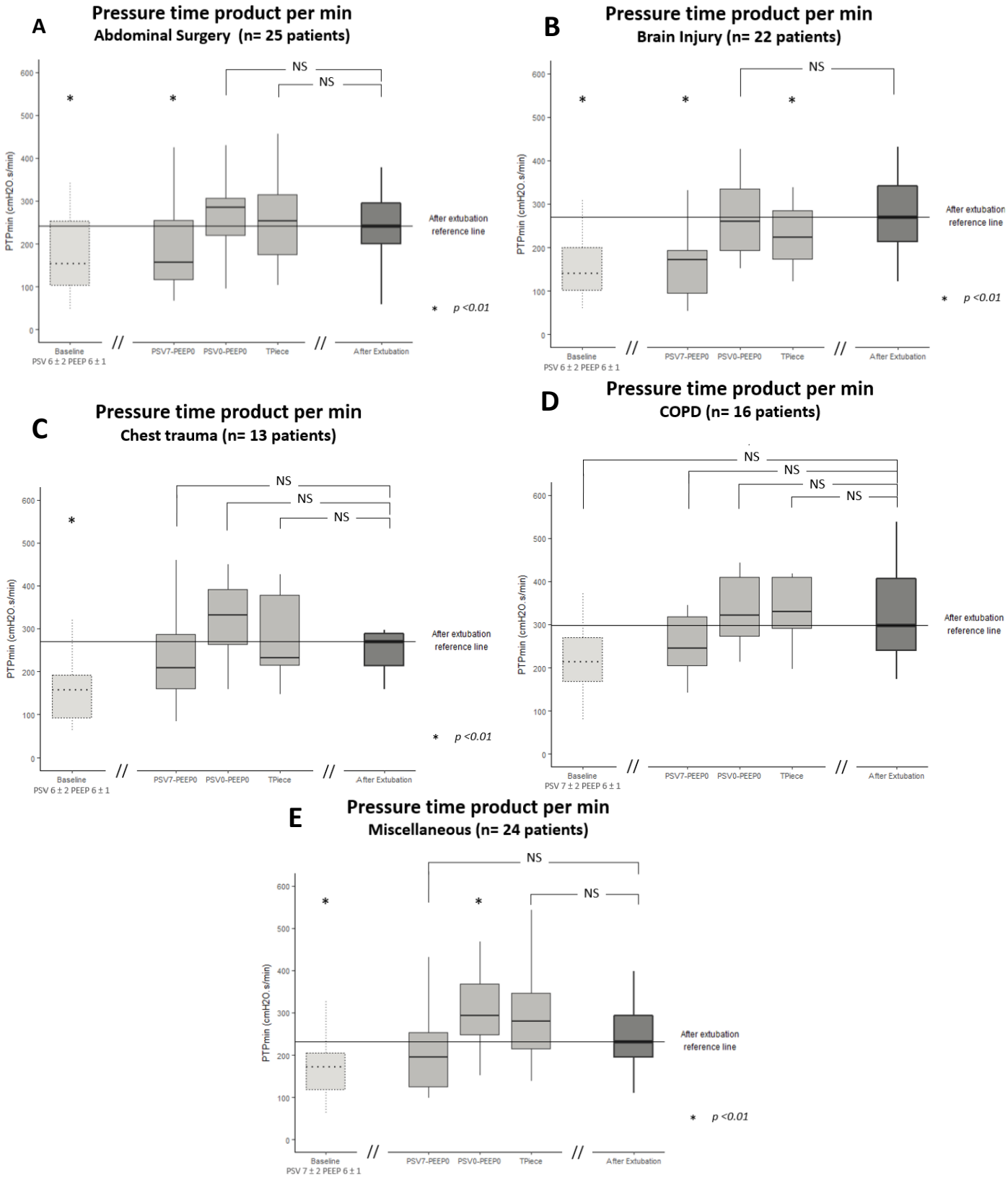


Figure 2: Pressure time product per minute (PTPmin) obtained at baseline, at the end of the three spontaneous breathing trials and 20 minutes after extubation according to the five phenotypes of patients: (A) post operative of abdominal surgery, (B) brain injury, (C) chest trauma, (D) chronic obstructive pulmonary disease (COPD) exacerbation and (E) miscellaneous patients.



CONCLUSION ET PERSPECTIVES

Au cours de ce travail de thèse nous avons défini les composantes structurelles et fonctionnelles du muscle diaphragmatiques, son rôle et son importance dans la fonction respiratoire. Nous avons rappelé la physiopathologie de la dysfonction diaphragmatique à partir des connaissances établies à ce jour. Nous avons rappelé son incidence élevée chez le patient de réanimation, et son impact sur le sevrage ventilatoire. Nous avons présenté les outils à notre disposition pour son diagnostic. Nous avons aussi évoquer les pratiques et les écueils concernant l'épreuve de ventilation spontané pour estimer l'effort respiratoire demandé au patient après extubation.

La première problématique était de poursuivre les avancées dans la compréhension de la physiopathologie de la dysfonction diaphragmatique, notamment lors de phase de reprise d'activité spontanée. La seconde problématique était de développer un outil simple et disponible pour démocratiser l'évaluation de la fonction diaphragmatique au chevet du patient, mais aussi d'améliorer les outils déjà en place. La troisième problématique était de redéfinir et réévaluer les pratiques concernant les épreuves de ventilation spontanée, dans le spectre de la réanimation moderne, avec un objectif de personnalisation du sevrage selon la pathologie.

Les travaux réalisés montrent premièrement qu'une ventilation assistée inadaptée associant sous-assistance et dyssynchronie, entraine une altération fonctionnelle et structurelle du diaphragme de façon importante et rapide. D'un point de vue structurel il s'agit essentiellement d'une distorsion de l'architecture sarcomérique associant déchirures et élongations. Dans un second temps nous avons valider un outil simple de stimulation diaphragmatique électrique associé à un repérage échographique du nerf phrénique pour le diagnostic de dysfonction diaphragmatique. Nous avons aussi établi que l'échographie peut être agrémenté de l'élastographie pour être plus précis dans l'évaluation notamment qualitative et structurelle du muscle diaphragmatique. Enfin troisièmement nous avons pu voir que les épreuves de ventilation spontanée sans assistance étaient les plus à même d'estimer l'effort

respiratoire qui sera demandé au patient après extubation, mais que cela peut varier sur la pathologie du patient.

Pour le futur nous prévoyons de poursuivre les explorations physiopathologiques de la dysfonction diaphragmatique liée à la ventilation assistée, avec l'aide de modèles porcins cette fois-ci malades, pour se rapprocher encore plus des conditions cliniques. Nous allons poursuivre le développement de notre outil de stimulation phrénique en optimisant la transmission électrique afin de diminuer l'ampérage nécessaire et de le rendre plus simple à utiliser chez le patient conscient. Nous allons aussi améliorer la mesure de pression trachéale après stimulation pour pouvoir l'utiliser sur tout respirateur et aller encore plus vers la démocratisation de l'outil. Enfin nous prévoyons de réaliser un essai contrôlé randomisé pour laquelle une demande de PHRC a été déposé et qui comparerait l'épreuve de ventilation spontanée AI 0 cmH2O PEP 0 cmH2O versus l'épreuve avec pièce en T. L'avantage de l'épreuve AI 0 PEP 0 étant la persistance de l'humidification, le monitorage des volumes et de l'EtCO2, l'absence de débranchement et donc diminution du risque d'erreurs et transmission infectieuse.

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TRAVAUX SCIENTIFIQUES

Impact of inadequate assisted ventilation on diaphragm function and structure

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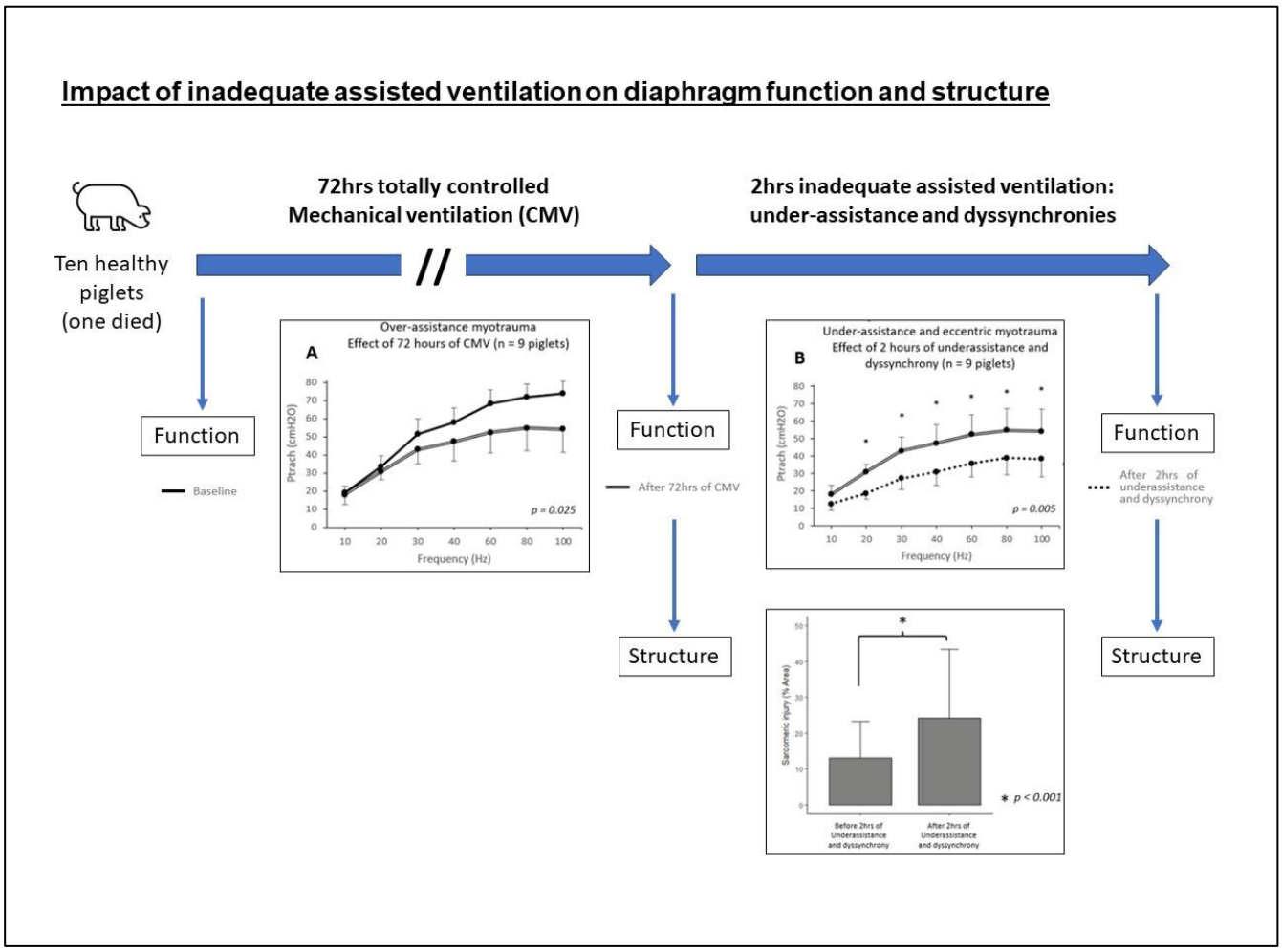
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Words count abstract n= 266
Words count body manuscript n= 2812
References n= 28
Tables n=1 ; Figures n=4
Appendix Supplemental: Tables n=3 ; Figures n=5

This article has an online data supplement, which is accessible from this issue's table of content online at https://ccforum.biomedcentral.com/

VISUAL ABSTRACT



ABSTRACT

Background: Inadequate assisted ventilation following prolonged invasive mechanical ventilation is common and associated with extubation failure, extended length of stay and mortality. The direct impact of inadequate assisted ventilation combining underassistance and dyssynchrony on diaphragm function and structure after prolonged invasive mechanical ventilation is unknown. The objective of the study was to assess the effect of under-assisted mechanical ventilation and dyssynchrony after prolonged totally controlled mechanical ventilation (CMV) on diaphragm function and structure in a piglet model.

Methods: Ten Large-White piglets were sedated and maintained under CMV during 72 hours followed by 2 hours of spontaneous ventilation modes with under-assisted mechanical ventilation and dyssynchrony. Diaphragm function (supramaximal diaphragm force assessed by negative tracheal pressure after transvenous phrenic nerve stimulation) was recorded at baseline (start of sedation), after 72 hours of CMV and after 2 additional hours of inadequate assisted ventilation. Diaphragm structure (sarcomeric injury) was evaluated by electron microscopy from biopsies harvested after 72 hours of CMV and after 2 additional hours of inadequate assisted ventilation.

Results: Supramaximal diaphragm force decreased by 22% from 69.9±12.7 to 54.9±19.7 cmH2O (p=0.025) after 72 hours of CMV attesting ventilatory-induced-diaphragm-dysfunction (VIDD). It dropped by an additional 29% from 54.9±19.7 to 38.9±15.5 cmH2O (p<0.005) after 2 hours of inadequate assisted ventilation. Diaphragm sarcomeric injuries accounted for 13±10% of the total micrograph area after 72 hours of CMV and increased to 24±19% (p<0.001) after 2 hours of inadequate assisted ventilation.

Conclusions: Two hours of under-assisted mechanical ventilation and dyssynchrony in pre-existing VIDD are associated with further impairment of diaphragm function and additional damage to the diaphragm structure in this experimental piglet model.

Keywords: Mechanical Ventilation, Dyssynchrony, Ventilator-Induced Diaphragm Dysfunction, Myotrauma

INTRODUCTION

Mechanical ventilation is a life-saving intervention and the main organ support in intensive care units (ICU). However, it is a two-edged sword. Inappropriate ventilator settings can induce ventilator-induced lung injury (1) and ventilator-induced diaphragm dysfunction (VIDD) (2). After recovery from acute illness, reducing sedation and achieving patient-adapted ventilation is a challenging process, with a delicate balance between over-assistance and under-assistance (3).

A major issue is to ensure synchronized ventilation between patient and ventilator. Severe patient-ventilator dyssynchrony is quite common following prolonged invasive mechanical ventilation (IMV) with 11% to 26% of patients affected (4–7) and is associated with extended ICU length of stay (5,6), with more extubation failure (7) and higher ICU and hospital mortality (5,8). Various forms of patient-ventilator dyssynchrony can induce harmful eccentric diaphragmatic contraction such as ineffective triggering, premature cycling and reverse triggering (9–12).

VIDD due to over-assistance myotrauma (insufficient muscle loading) is well documented (13–20). The impact of under-assistance myotrauma (excess muscle loading) and eccentric myotrauma (due to dyssynchrony) on diaphragm structure and function remains controversial and speculative. Two recent experimental studies (21,22) performed in a porcine model of acute respiratory distress syndrome (ARDS) did not clearly demonstrate diaphragmatic impairment after dyssynchrony. Damiani et al (21) showed that only animals with high breathing effort exhibit decreased diaphragm force with muscle injury. Noteworthy, both porcine models did not undergo prolonged passive IMV before dyssynchrony in these two experiments (21,22).

To our knowledge there is no study evaluating the impact of inadequate assisted ventilation with under-assisted mechanical ventilation and dyssynchrony on diaphragm function and structure after prolonged IMV. We aimed to develop a pragmatic piglet model reflecting the

clinical conditions with prolonged passive IMV and inadequate assisted ventilation upon sedation reduction, in order to assess its impact on diaphragm function and structure. We hypothesized that under-assisted mechanical ventilation and severe subject-ventilator dyssynchrony, in case of pre-existing VIDD due to prolonged passive IMV, generates further impairment of diaphragm function and additional damage to the diaphragm structure.

MATERIAL AND METHODS

Study Design

We performed an experimental study in a piglet model of prolonged totally controlled mechanical ventilation (CMV) for 72 hours followed by an additional 2 hours of inadequate assisted ventilation with under-assisted mechanical ventilation and dyssynchrony. The Institutional (University of Montpellier, France) and the Regional (CEEA-LR-36) Ethics Committees for Animal Research and Care, and the French Ministry of Agriculture (Paris, France) approved the study protocol (APAFIS #15866 2018070509081002). All experiments were conducted in an authorized laboratory under the supervision of authorized researchers (SJ, SM, BJ), and complied with the Animal Research Reporting of *In Vivo* Experiments (ARRIVE) guidelines (**Supplementary material**). Detailed methods are described in the online supplement.

Experimental Protocol

The experimental protocol with timeline is summarized in **Figure 1**. Piglets were under CMV for 72 hours and then were exposed to 2 hours of under-assisted mechanical ventilation and dyssynchrony. Thus, the total duration of invasive mechanical ventilation was 74 hours. The diaphragm function was recorded at baseline (start of sedation), after 72 hours of CMV, and after the additional 2-hours period of under-assisted mechanical ventilation and dyssynchrony. A minimally invasive diaphragm biopsy was harvested after 72 hours of CMV and after the additional 2 hours of under-assisted mechanical ventilation and dyssynchrony to observe diaphragm structure.

Two piglets were anesthetized at the same time in each session. Doctor and nurse tandems trained in critical care medicine and animal experiments provided round-the-clock supervision, monitoring, and animal care, alternating 12-hour shifts for the entire duration of the study.

Piglet Model

Ten Large-White piglets (29±2 kg) were sedated with propofol, midazolam, ketamine and sufentanil, to ensure proper anesthesia, adequate ventilation without dyssynchrony and stable hemodynamics. No neuromuscular blocking agent were used. After orotracheal intubation with a cuffed endotracheal tube, the piglets were mechanically ventilated in volume-controlled mode with tidal volume (VT) of 10±2 ml kg^{-1} and respiratory rate (RR) of 20 to 30 min^{-1} to achieve physiologic hematosis and to avoid dyssynchrony. The positive end-expiratory pressure (PEEP) was initially set at 5 cmH_2O, and the oxygen fraction (FiO_2) was adjusted to obtain a partial pressure of oxygen (P_aO2) from 60 to 90 mmHg.

The experimental design was similar to our previously reported experimental studies (14–16,23). Briefly: the right femoral artery, femoral vein, and urinary bladder were catheterized. Cardiac output was monitored by a pulse contour cardiac output system (PiCCO®, Pulsion Medical System, Germany). An oral gastric tube was inserted for enteral nutrition. An air-filled balloon-tipped esophageal catheter (Marquat, Boissy-Saint-Léger, France) was placed transorally in the distal third of the esophagus. Bipolar transvenous pacing catheters (PVC, 6 Fr, Bard, France) were introduced via each internal jugular vein and adjusted to achieve stimulation of the phrenic nerve and subsequent contraction of the diaphragm (**Figure S1**). At the end of the experiment, piglets were euthanized with barbiturate overdose.

Heart rate (HR), systolic, diastolic and mean arterial blood pressures (SAP, DAP and MAP), cardiac output (CO), and oxygen saturation (SpO_2) were continuously monitored. VT and minute volume ventilation were also measured continuously. Blood gases with serum creatinine were measured several times a day using a point of care analyzer (Epoc, Siemens, Erlangen, Germany).

Induction and assessment of under-assisted mechanical ventilation and dyssynchrony

After 72 hours of CMV, the sedation was stopped until spontaneous ventilation was observed, and then titrated to obtain spontaneous breathing without consciousness. Piglets were switched to ventilation modes that allowed spontaneous breathing and then experienced 2 hours of underassistance and induced dyssynchrony.

First, the ventilator was set in asynchronous intermittent mandatory ventilation mode (without trigger) with gradual decrease of RR to the lowest tolerated by the piglets with a target of 5 per minute. To induce under-assistance myotrauma, there was no pressure support for spontaneous cycles. The other respiratory parameters such as VT or PEEP were not modified. As in clinical practice, the ventilator was then switched to pressure support mode. To induce eccentric myotrauma, a high expiratory trigger sensitivity value of 70% of peak inspiratory flow was set leading to premature cycling. The pressure support level was optimized to obtain a VT of 8-10 ml kg^{-1}. The PEEP was not modified. During the 2 hours of underassistance and induced dyssynchrony, we regularly alternated the two ventilatory modes.

The inspiratory effort during the inadequate assisted ventilation period could differ among piglets, with a potentially different impact on diaphragm impairment (21). Piglets were thus divided into three groups according to the level of breathing effort using mean swing esophageal pressure (P_{es}) terciles.

Flow, airway pressure (P_{aw}) and P_{es} were recorded using a pneumotachograph and a differential pressure transducer (TSD 160, Biopac Systems, Goleta, CA). We selected a representative 5-minutes tracing (21) of each ventilation mode at the end of the 2 hours of under-assisted mechanical ventilation and dyssynchrony period (**Figure 2**) to collect data on physiological variables, ventilatory characteristics and respiratory mechanics.

Diaphragm Function

To assess diaphragm function, we used bilateral phrenic nerve stimulation to obtain a negative tracheal pressure after airway occlusion (Ptrach) (14–16,23). A Stimep Neurostimulator (Axonic, Vallauris, France) was connected to the pacing catheters for stimulation. All measurements were obtained from sedated piglets in a supine position, with end expiratory pressure of 0 cmH2O.

As previously described (14–17), a force frequency curve was obtained by stimulating end-expiratory diaphragm contractions with occluded airways using supramaximal phrenic nerve stimulation with a stimulus duration of 0.15 ms and a train duration of 2000 ms. Contractions were obtained at fixed frequencies of 10, 20, 30, 40, 60, 80, and 100 Hz. We ensured a 2-minute rest period between each frequency.

Diaphragm Structure

Mini-invasive muscle biopsies were harvested by surgical team from the right sub-costal diaphragm after 72 hours of CMV and after the 2-hours of inadequate assisted ventilation period for each piglet. Samples of dissected diaphragm strips were immediately fixed for electron microscopy examination. Detailed methods are described in the online supplement.

Computer images captured from randomly selected microscopic fields were analyzed by two independent observers blinded to group allocation. A total of 12 micrographs per piglet were examined, 6 from diaphragm before inadequate assisted ventilation and 6 from diaphragm after inadequate assisted ventilation. The percentage of area including sarcomeric injuries was determined by a standardized stereology grid method (24) using ImageJ® software. As described in previous study (13), disrupted sarcomeres were defined as a zone with distinct distortion of the usual sarcomeric architecture.

Statistical Analysis

All statistical analyses were performed using R software 3.6.2 (R Project for Statistical Computing). All *p* values were two-tailed, and a *p* value of less than 0.05 was required to rule out the null hypothesis. After performing a Shapiro-Wilk test to ensure the normality of the variables distribution, we expressed data as mean ± SD. Comparison of two means was performed using a paired Student t-test. For diaphragm function assessment, comparison between groups and changes along stimulation frequency were performed by two-way ANOVA. Repeated measures analysis of variance and multiple paired t-test were applied for post hoc analysis with Bonferroni correction.

RESULTS

Piglet Model

Of all the piglets, initially healthy, one died of sudden cardiac arrest following severe ARDS and was therefore excluded. The others 9 piglets completed the experiment. All characteristics with hemodynamic, respiratory, metabolic values and sedation dose are presented in **Figure S2**. There were no significant dyssynchrony events during the prolonged CMV period.

Inadequate assisted ventilation

The 5-minutes selected tracing from the end of the 2 hours of underassistance and dyssynchrony period revealed a rate of unassisted and dyssynchronous respiratory cycles (over all cycles) ranging from 30% to 73% according to piglet. The inspiratory effort during this 5-minutes selected tracing varies from 2.7±0.4 cmH_2O to 13.6±1.2 cmH_2O per cycle according to piglet (**Table 1**). Detailed ventilatory characteristics and respiratory mechanics are presented in **Table S1** and **Table S2**. There was no correlation between dyssynchrony index and inspiratory effort (**Figure S3**). Piglets were divided into three groups according to inspiratory effort (**Figure S4**).

Hematosis disorders were reported after underassistance and dyssynchrony with a significant difference compared to before underassistance and dyssynchrony (**Table S3**). There was no significant difference in hemodynamic values except for a higher heart rate. There was no significant difference in sedation.

Diaphragm function

After 72 hours of CMV the force frequency curve showed a decrease in supramaximal diaphragm force of 22%, from 69.9±12.7 to 54.9±19.7 cmH2O (p=0.025). After 2 additional hours of inadequate assisted ventilation the supramaximal diaphragm force dropped by an

additional 29%, from 54.9±19.7 to 38.9±15.5 cmH2O (p=0.005) (**Figure 3**). This fall did not correlate with the level of inspiratory effort (**Figure S5**).

Diaphragm structure

After 72 hours of CMV, diaphragm sarcomeric injuries represented 13±10% of total area of the micrographs. This rate rises to 24±19% after 2 additional hours of inadequate assisted ventilation with significant difference (p<0.001) (**Figure 4**). This alteration of diaphragm structure did not strongly correlate with the level of inspiratory effort (**Figure S5**). The diaphragm samples were analyzed with excellent agreement between the two observers (intraclass correlation coefficient > 0.9).

DISCUSSION

Two hours of under-assisted mechanical ventilation and severe subject-ventilator dyssynchrony in pre-existing VIDD due to prolonged passive IMV are associated with further impairment of diaphragm function and additional damage to the diaphragm structure in this experimental piglet model. There was no significant difference according to level of inspiratory effort.

To our knowledge this is the first time we have shown the harmful effect of combining over-assistance myotrauma with under-assistance and eccentric myotrauma.

Piglet model

Recent similar experimental studies with piglet models have not shown diaphragm impairment after 12 hours of ineffective efforts and double triggering (22), or after 3 hours of reverse triggering (21) except for piglets with high breathing effort. Dyssynchrony index was high in these two studies but the severe subject-ventilator dyssynchrony period started directly after animal preparation. The absence of prolonged CMV before probably explains the difference with our results. A diaphragm impaired by pre-existing VIDD appears more prone to be affected by dyssynchrony.

Our piglet model of prolonged CMV, with transvenous phrenic nerve stimulation for diaphragm function assessment, was developed in our previous experiments (14–17). This time we added a 2-hour period of under-assisted mechanical ventilation and severe dyssynchrony after reducing sedation and using simple unsuitable respiratory parameters. Our aim was to amplify what could happen in clinical practice. After a period of sedation and passive IMV, the ICU patient is awakened, then underassistance and dyssynchrony may appear and persist without being detected, nor the ventilatory parameters adapted, with potential damage to the diaphragm, as described in the present study.

Diaphragm impairment

There are four distinct types of diaphragmatic myotrauma (11). First, over-assistance myotrauma, disuse atrophy due to insufficient muscle loading. Second, under-assistance myotrauma, sarcomeric injuries and contractile fatigue due to excessive muscle loading. Third, eccentric myotrauma, contractile stress delivered to the muscle when it is lengthening (eccentric loading), induced by dyssynchrony (ineffective effort, premature cycling, reverse triggering). Fourth, expiratory myotrauma, contractile stress delivered after PEEP withdrawal on a reduced diaphragm (longitudinal atrophy) due to prolonged excessive PEEP. The concept of under-assistance and eccentric myotrauma is rather recent (3,9,11) and the direct impact on the diaphragm is not clearly established. Our study provides substantial data on the topic with a focus on diaphragm with pre-existing VIDD due to prolonged passive IMV.

The absence of correlation between diaphragm impairment and level of breathing effort could be explained by the alteration of diaphragm force due to prolonged CMV. A low breathing effort could be due to VIDD with potentially increased susceptibility to dyssynchrony injuries.

Limitations

Our study has several limitations. First, we did not add a group with prolonged passive IMV followed by synchronized pressure support ventilation (without inadequate assisted ventilation). We considered that adapted spontaneous breathing after prolonged passive IMV does not impair diaphragm function as previously describe in a murine model (25). Secondly, there are two potential confounding factors of diaphragm impairment. The severe hypercapnic acidosis, result of inadequate assisted ventilation, whose effect on altering the piglet diaphragm contractility has already been demonstrated (15). However, it cannot be responsible for the additional damage to the diaphragm structure. It should be remembered that moderate hypercapnia has a protective effect (17,26). Then, the impact of the minimally invasive diaphragm biopsy could also affect the results. Thirdly, we recorded only a 5-minutes tracing

representative of each pattern at the end of the 2 hours of inadequate assisted ventilation period. We considered a certain stability of the underassistance and dyssynchrony during this period. Fourthly, some piglets were ventilated with high VT during the IMV period that did not reflect the standard of care. Our aim was to avoid dyssynchrony during this period, which has previously been shown to be difficult with low tidal volume (21). Fifthly, there was no measurement of end-expiratory lung volume (EELV). It has never been demonstrated, but it could affect the diaphragm conformation and thus the impact of eccentric contractions. Sixthly, the choice of tracheal pressure instead of transdiaphragmatic pressure could be questioned. Measurements of diaphragm function were performed on sedated subjects, we thus considered gastric pressure to be low with minimal influence on diaphragm function assessment. Also, we chose swing P_{es} instead of pressure time product (PTP) for assessing the level of breathing effort. Some piglets had a high respiratory rate, making the PTP measurement difficult to perform and unreliable.

Clinical implications and perspectives

This study provides additional data on the impact of the under-assistance and eccentric myotrauma induced by dyssynchrony, and arguments to encourage lung and diaphragm protective ventilation (27). After prolonged IMV, the switch to assisted ventilation should be made with caution, with adequate pressure support and parameters to avoid under assistance and dyssynchrony. In case of fast weaning process, the same precautions should be taken when performing a spontaneous breathing trial. To go further, we could investigate whether there is the same impact of under-assisted ventilation and dyssynchrony on diaphragm function after a short period of passive ventilation. Wittenstein et al. in their experiment of ARDS piglets with dyssynchrony after a short passive ventilation (22) did not assess the diaphragm function. We could evaluate the impact of dyssynchrony after prolonged CMV with a piglet model of ARDS, sepsis, trauma, post operative status. We could evaluate the impact of different sorts of dyssynchrony patterns alone, with different levels of dyssynchrony rate. We

could assess the impact of diaphragm conformation with different levels of PEEP and EELV. We could improve our experimental model with the implementation of a minimally invasive extracorporeal CO2 removal as described previously (28) to eliminate hypercapnic acidosis as a confounding factor and validate our results.

CONCLUSION

In this experimental study with a piglet model, we reported that two hours of under-assisted mechanical ventilation and severe subject-ventilator dyssynchrony, in the setting of pre-existing VIDD, are associated with further impairment of diaphragm function and additional damage to the diaphragm structure. Further research is needed to confirm these findings, with animal model under different conditions to understand the mechanism, in patients to assess clinical impact.

DECLARATIONS

ETHICS APPROVAL

The Institutional (University of Montpellier, France) and the Regional (CEEA-LR-36) Ethics Committees for Animal Research and Care, and the French Ministry of Agriculture (Paris, France) approved the study protocol (APAFIS #15866 2018070509081002).

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

Data are available from the corresponding author on reasonable request.

COMPETING INTERESTS

SJ reports receiving consulting fees from Drager, Mindray, Medtronic, Baxter, Fresenius-Xenios and Fisher & Paykel. ADJ reports receiving consulting fees from Drager, Medtronic and Fisher & Paykel. LB's lab has received research grants from Medtronic, Drager and Stimit and equipment from Sentec, Fisher & Paykel and Philips and lecture fees from Fisher & Paykel. No potential conflict of interest relevant to this article was reported for other authors.

FUNDING

Inserm Transfert (COPOC program).

AUTHOR'S CONTRIBUTIONS

MC and SJ designed the study. MC, YA, JP, LD, TS, AC and FR performed the intervention and acquired the data. MC, ADJ, NM and SJ contributed to data analysis. MC, BJ, JC, JYLG, FR, SM, LB AL and SJ were involved in data interpretation. MC, ADJ, JC and SJ drafted the manuscript and all authors reviewed it. All authors approved the final version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGMENTS

We thank all the teams of Department of Anesthesiology and Critical Care Medicine B (DAR B), Saint-Eloi Hospital. We thank all the teams of the laboratory PhyMedExp. We thank the surgical team of Saint-Eloi Hospital and especially Dr Bader Al Taweel. We would like to thank the technical platform of experimental research of Nimes (RAM-PTNIM) and Mrs Marylène Bacle for her precious help. We would like to thank the Institute of Neuroscience of Montpellier (INM) and Mrs Chantal Cazevieille for her help in electron microscopy examination. We would like to thank Dr. July Beghin for her contribution to the analysis of electron microscopy images.

ABBREVIATIONS

ARDS: Acute respiratory distress syndrome.

CMV: Controlled mechanical ventilation.

CO: Cardiac output.

DAP: Diastolic arterial pressure.

EELV: End expiratory lung volume.

FiO2: Inspired oxygen fraction.

HR: Heart rate.

ICU: Intensive care unit.

IMV: Invasive mechanical ventilation.

MAP: Mean arterial pressure.

PaO2: Partial pressure of oxygen.

Paw: Airway pressure.

PEEP: Positive end expiratory pressure.

Pes: Esophageal pressure.

PTP: Pressure time product.

Ptrach: Tracheal pressure.

RR: Respiratory rate.

SAP: Systolic arterial pressure.

SpO2: Pulse oxygen saturation.

VIDD: Ventilator induced diaphragm dysfunction.

VT: Tidal volume.

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FIGURE LEGENDS

- **Figure 1:** experimental study design, timeline of interventions and measurements. After starting sedation and animal preparation, the piglets were under totally controlled mechanical ventilation (CMV) for 72 hours. The sedation was then stopped until spontaneous ventilation was observed, and finally titrated to obtain spontaneous breathing without consciousness. The ventilation was switched to allowed spontaneous breathing. Piglets were exposed to an additional 2 hours of under-assisted mechanical ventilation and dyssynchrony. Diaphragmatic function, hemodynamic and respiratory variables were recorded at baseline (start of sedation), after 72 hours of CMV, and after the additional 2-hour period of inadequate assisted ventilation. A minimally invasive diaphragm biopsy was harvested after 72 hours of CMV and after an additional 2-hours of inadequate assisted ventilation for diaphragm structure observation. A 5-minutes representative respiratory tracing was recorded at the end of the inadequate assisted ventilation period.
- **Figure 2:** illustration of selected representative respiratory tracings from spontaneous breathing patterns observed on a same piglet: (*A*) unassisted effort and (*B*) dyssynchrony with double triggering. Airway pressure (Paw), flow, and esophageal pressure (Pes) tracing are presented in red, blue, and green lines respectively. (*A*) During the unassisted effort (excess muscle loading), spontaneous patient's inspiratory effort (negative esophageal pressure) occurred during expiratory phase without ventilator assistance (no pressure support). (B) During the double triggering pattern, first there was a premature cycling, the airway pressure and flow returned to baseline (flow starvation) even though the inspiratory effort is still in progress (negative esophageal pressure, eccentric contraction), and second a new insufflation is triggered by the persistent spontaneous inspiratory phase. *Paw: airway pressure. Pes: esophageal pressure.*

- **Figure 3:** diaphragmatic force frequency curves (*A*) at baseline versus after 72 hours of totally controlled mechanical ventilation (CMV), (*B*) and after 72 hours of CMV versus after 2 additional hours of inadequate assisted ventilation, for the same piglets (n=9). Force-frequency curves illustrates supramaximal diaphragm force represented by negative tracheal pressure in airway occlusion condition (Ptrach), after different frequencies of bilateral phrenic nerve stimulation. After 72 hours of CMV the force frequency curve showed a decrease in supramaximal diaphragm force of 22% and after 2 additional hours of inadequate assisted ventilation the supramaximal diaphragm force dropped by an additional 29%. *CMV: Totally controlled mechanical ventilation. Ptrach: tracheal pressure. Posted p-values between two periods were obtained after two-way ANOVA. * p<0.01 between two periods using paired t-test with Bonferroni correction for post hoc analysis.*
- **Figure 4:** Representative electron microscopy images of longitudinal ultrathin sections obtained from the diaphragms after 72 hours of CMV (A) before and (B) after 2 additional hours of inadequate assisted ventilation. (C) Percentage area of diaphragm sarcomeric injury after 72 hours of totally controlled mechanical ventilation (CMV), before versus after 2 additional hours of inadequate assisted ventilation. White arrows show disorganization of sarcomeric structure. White arrows show disorganization of sarcomeric structure. After 72 hours of CMV, diaphragm sarcomeric injuries represented 13±10% of total area of the micrographs. This rate rises to 24±19% after 2 additional hours of inadequate assisted ventilation. *CMV: Totally controlled mechanical ventilation. Posted p-values between two periods was obtained after paired t-test. * p<0.05 between two periods.*

TABLES

Table 1: individual values and mean values of unassisted and dyssynchronous respiratory cycles rate and inspiratory efforts.

Piglet	Unassisted and dyssynchronous respiratory cycle rate (%)	Swing P_{es} (cmH_2O)*
Piglet 1	59	3.3 (±0.6)
Piglet 2	61	10.4 (±0.6)
Piglet 3	39	9.5 (±1.4)
Piglet 4	73	10.6 (±0.8)
Piglet 5	68	2.7 (±0.4)
Piglet 6	42	2.9 (±0.2)
Piglet 7	30	10.7 (±1.8)
Piglet 8	67	13.6 (±1.2)
Piglet 9	52	8.9 (±1.2)
Total	54 (±15)	8 .1 (±4.0)

**Data are presented as mean (±Standard Deviation)*
Abbreviations. P_{es}: esophageal pressure

FIGURES

Figure 1: experimental study design.

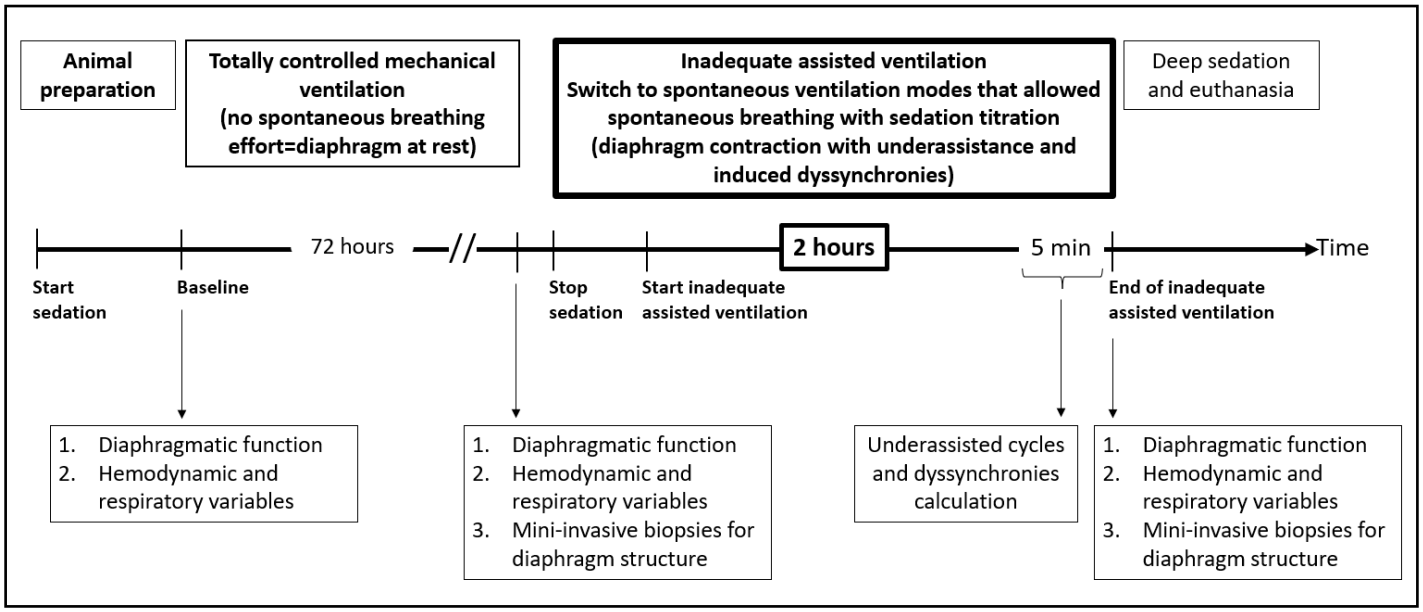


Figure 2: illustration of selected representative respiratory tracings from spontaneous breathing patterns observed on a same piglet.

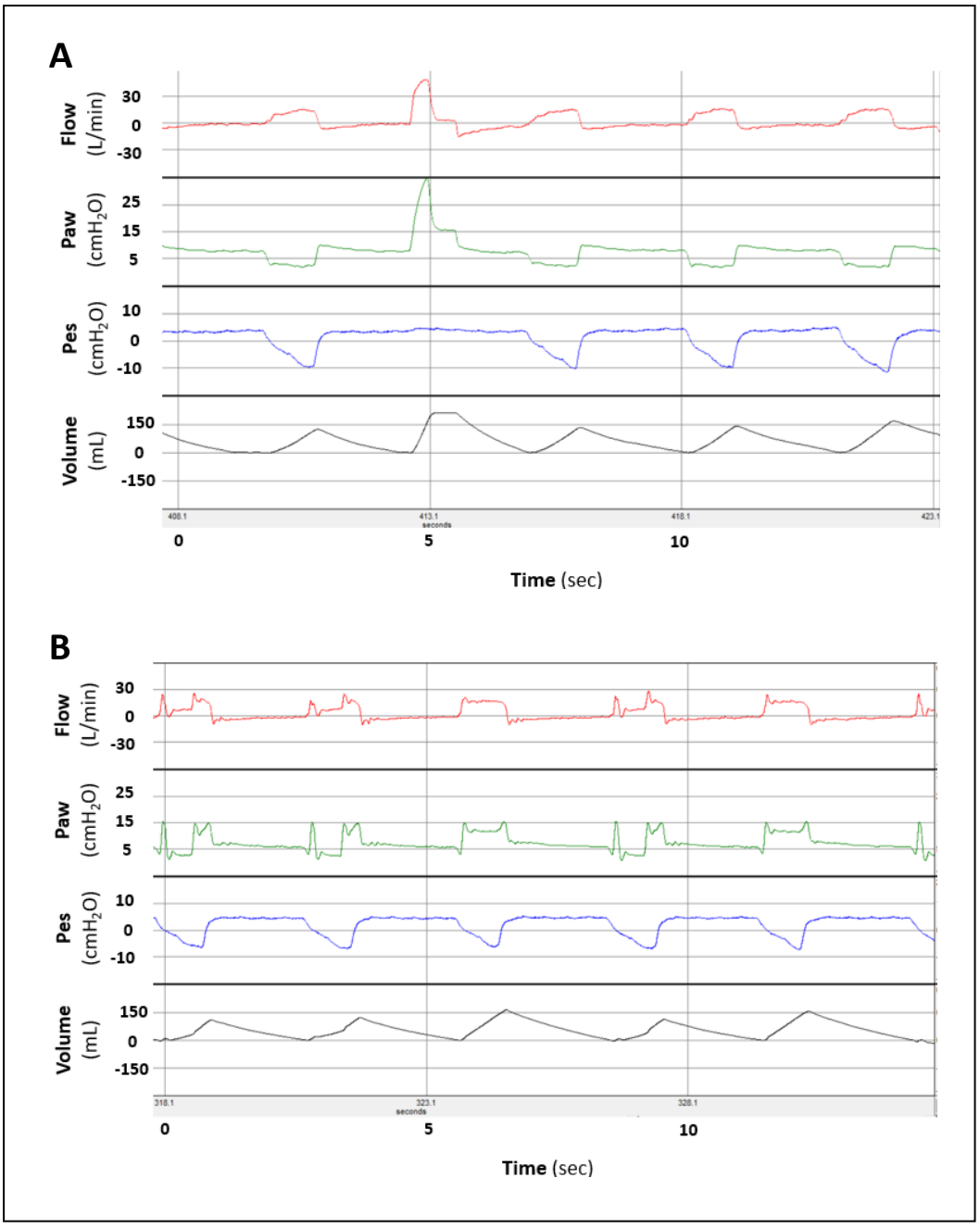


Figure 3: function assessment with diaphragmatic force frequency curves.

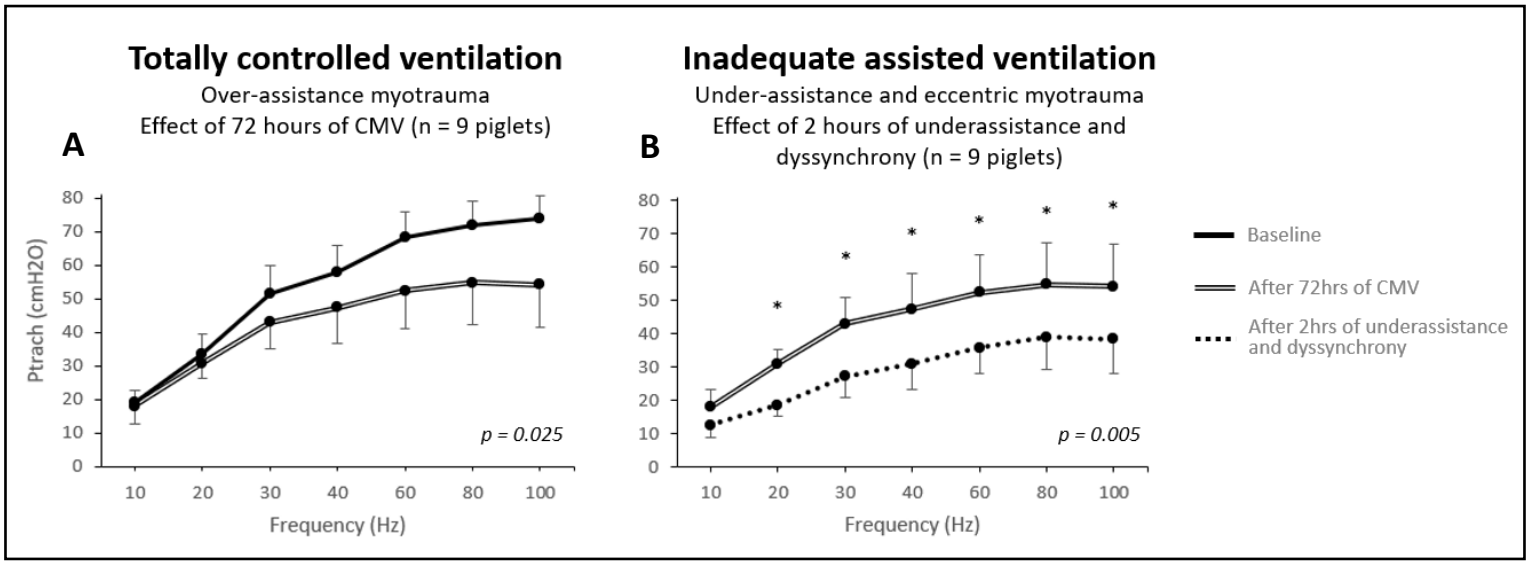
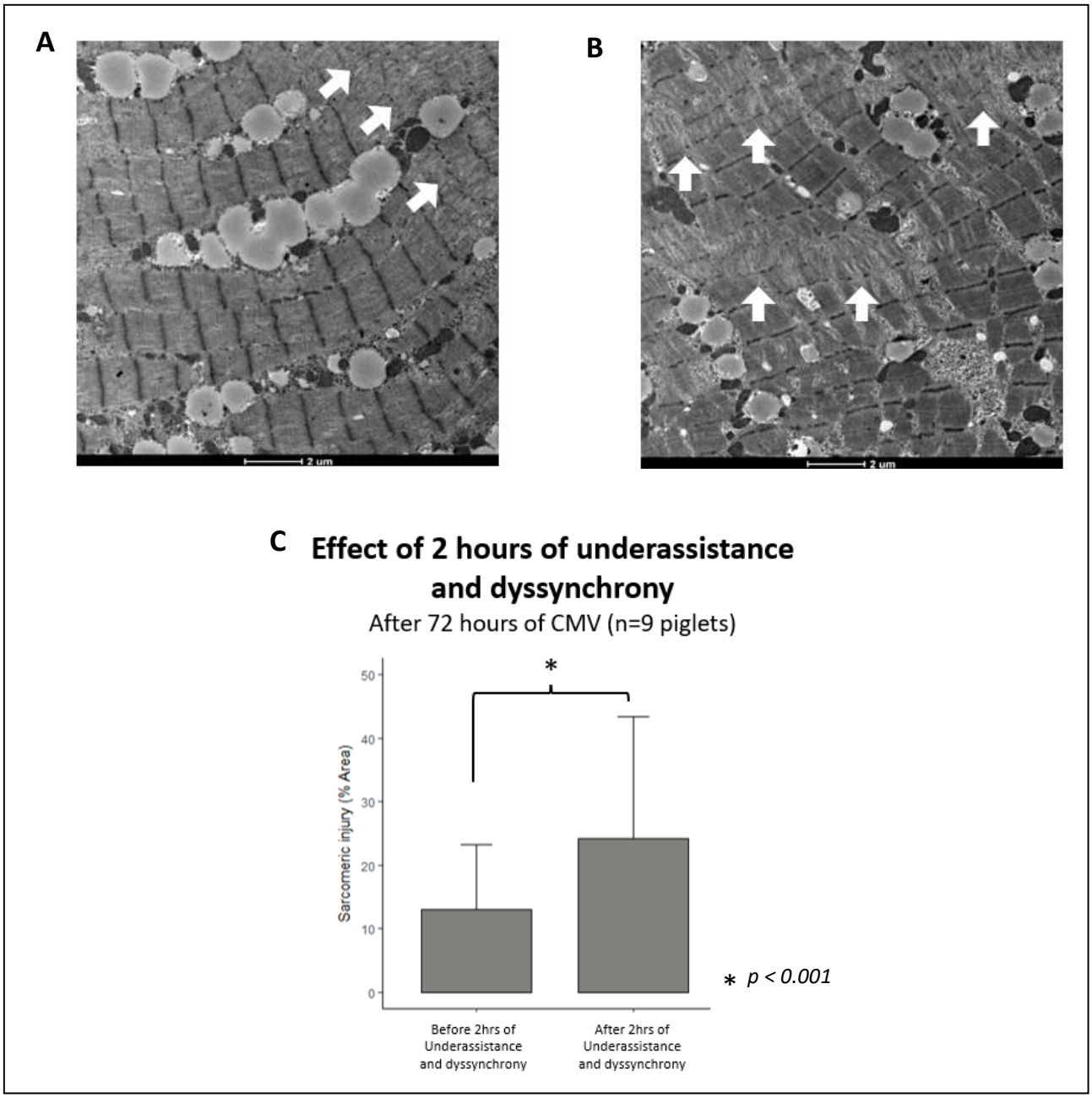


Figure 4: structure assessment with percentage area of diaphragm sarcomeric injury.



SUPPLEMENTARY MATERIAL

Impact of inadequate assisted ventilation on diaphragm function and structure

Mathieu Capdevila, Audrey De Jong, Boris Jung, Yassir Aarab, Joris Pensier, Lucas Deffontis, Thomas Sfara, Ambre Cuny, Julie Carr, Nicolas Molinari, Jean-Yves Le Guennec, Fabrice Raynaud, Stefan Matecki, Laurent Brochard, Alain Lacampagne, Samir Jaber

SUPPLEMENTAL METHODS

Study Design

We performed an experimental study in a piglet model of prolonged totally controlled mechanical ventilation (CMV) for 72 hours followed by 2 additional hours of inadequate assisted ventilation with underassistance and dyssynchrony. The Institutional (University of Montpellier, France) and the Regional (CEEA-LR-36) Ethics Committees for Animal Research and Care, and the French Ministry of Agriculture (Paris, France) approved the study protocol (APAFIS #15866 2018070509081002). All experiments were conducted in an authorized laboratory under the supervision of authorized researchers (SJ, SM, BJ), and complied with the Animal Research Reporting of In Vivo Experiments (ARRIVE) guidelines (**Supplementary material**).

Experimental Protocol

Piglets were under CMV for 72 hours and then were exposed to 2 hours of under-assisted mechanical ventilation and dyssynchrony. The total duration of invasive mechanical ventilation was 74h. The diaphragm function was recorded at baseline (start of sedation), after 72 hours of CMV, and after the additional 2-hour period of under-assisted mechanical ventilation and dyssynchrony. A minimally invasive diaphragm biopsy was harvested after 72 hours of CMV and after the additional 2 hours of under-assisted mechanical ventilation and dyssynchrony to observe diaphragm structure.

Two piglets were anesthetized at the same time in each session. Doctor and nurse tandems trained in critical care medicine and animal experiment provided round-the-clock supervision, monitoring, and animal care, alternating 12-hour shifts for the entire duration of the study.

Piglet Model

Ten Large-White piglets (29±2 kg) were sedated with intramuscular ketamine (3 $mg.kg^{-1}$), then a peripheral venous catheter was placed in an ear vein and anesthesia was induced with propofol (5 $mg.kg^{-1}$) and sufentanil (0.3 $\mu g.kg^{-1}$). After orotracheal intubation with a cuffed endotracheal tube, piglets were sedated with propofol, midazolam, ketamine and sufentanil, to ensure proper anesthesia, adequate ventilation without dyssynchrony, and well-stable hemodynamics. There was no use of neuromuscular blocking agents. Piglets were mechanically ventilated in volume-controlled mode with an Evita XL or Evita 2 Dura ventilator (Dräger®, Lübeck, Germany). Tidal volume (VT) was 10±2 ml kg^{-1} and respiratory rate (RR) 20 to 30 min^{-1} to achieve physiologic hematosis and to avoid dyssynchrony. The positive end-expiratory pressure (PEEP) was initially set at 5 cmH_2O, and the oxygen fraction (FiO_2) was adjusted to obtain a partial pressure of oxygen (P_aO2) from 60 to 90 mmHg.

We used the same experimental design (**Figure S1**) as previously described in our studies (E1–4). The right femoral vein was catheterized for blood sampling and administration of fluids and drugs. The right femoral artery was catheterized for pressures monitoring and cardiac output monitoring with a pulse contour cardiac output system (PiCCO®, Pulsion Medical System, Germany). An air-filled balloon-tipped esophageal catheter (Marquat, Boissy-Saint-Léger, France) was placed transorally in the distal third of the esophagus, filled with 4mL of air and connected to pressure transducer. The occlusion method was used to determine the location of the esophageal balloon. In addition, a pneumotachograph and transducer were placed at the proximal airway to assess airway pressure and flow. Prior to each experiment, the reproducibility of esophageal pressure measurements was evaluated by inspecting the waveform and performing an occlusion test prior to each experiment. Bipolar transvenous pacing catheters (PVC, 6 Fr, Bard, France) were introduced via each internal jugular vein and adjusted to achieve stimulation of the phrenic nerve and subsequent contraction of the diaphragm. An oral gastric tube was placed. Enteral nutrition (Nutrison® Energy 1.5 $kcal.ml^{-1}$;

Nutricia Saint Ouen, France) was started on day one and provided 30 $kcal.kg^{-1}.day^{-1}$. Vitamins and oligoelements were given on a regular basis. A vesicostomy was performed, and a urinary catheter was inserted to monitor urine output. Hourly body temperature measures were taken using a rectal probe, and the animals were resting on soft cushions. Heating pads were used as needed to keep the body temperature at 38.5° - 39.5°C. All procedures were performed in an aseptic manner. Prophylactic intravenous antibiotics (amoxicillin-clavulanate, 100 $mg.kg^{-1}.day^{-1}$) were given to the animals three times each day. All animals were given round-the-clock care, which included airway suctioning, turning, oropharyngeal lavage, and daily washing. At the end of the experiment, piglets were killed with barbiturate overdose.

Heart rate (HR), systolic, diastolic and mean arterial blood pressures (SAP, DAP and MAP), cardiac output (CO), and oxygen saturation (SpO_2) were continuously monitored. VT and minute volume ventilation were also measured continuously. Blood gases with serum creatinine were measured several times a day using a point of care analyzer (Epoc, Siemens, Erlangen, Germany).

Induction and assessment of under-assisted mechanical ventilation and dyssynchrony

After 72 hours of CMV, the sedation was stopped until spontaneous ventilation was observed, and then titrated to obtain spontaneous breathing without consciousness. Piglets was switched under ventilation modes that allowed spontaneous breathing and then experienced 2 hours of underassistance and induced dyssynchrony.

First, the ventilator was set in asynchronous intermittent mandatory ventilation mode (without trigger) with gradual decrease of RR to the lowest tolerated by the piglets with a target of 5 per minute. To induce under-assistance myotrauma, there was no pressure support for spontaneous cycles. The others respiratory parameters such as VT or PEEP were not modified. As in clinical practice, the ventilator was then switched to pressure support mode. To induce eccentric myotrauma, a high expiratory trigger sensitivity value of 70% of peak

inspiratory flow was set leading to premature cycling. The pressure support level was optimized to obtain a VT of 8-10 ml kg^{-1}. The PEEP was not modified. During the 2 hours of induced dyssynchrony, we regularly alternated the two ventilatory modes.

The inspiratory effort during the dyssynchrony period could differ among piglets, with a potentially different impact on diaphragm impairment (E5). Piglets were thus divided into three groups according to the level of inspiratory efforts based on measurements of swing in esophageal pressure (P_{es}).

Flow, airway pressure (P_{aw}) and P_{es} were recorded using a pneumotachograph and a differential pressure transducer (TSD 160, Biopac Systems, Goleta, CA). We selected a 5-minutes tracing (E5) representative of each ventilation mode at the end of the 2 hours of inadequate assisted ventilation period to collect data on physiological variables, ventilatory characteristics and respiratory mechanics.

Diaphragm Function

To assess diaphragm function, we used bilateral phrenic nerve stimulation to obtain a negative tracheal pressure after airway occlusion (Ptrach). A Stimep Neurostimulator (Axonic, Vallauris, France) was connected to the pacing catheters for stimulation. All measurements were obtained from sedated piglets in a supine position, with end expiratory pressure of 0 cmH2O.

As described in previous studies (E1,2,4,6), a force frequency curve was obtained by stimulating end-expiratory diaphragm contractions with occluded airways using supramaximal phrenic nerve stimulation with a stimulus duration of 0.15 ms and a train duration of 2000 ms. Contractions were obtained at fixed frequencies of 10, 20, 30, 40, 60, 80, and 100 Hz. We ensured a 2-minute rest period between each frequency.

Diaphragm Structure

Mini-invasive muscle biopsies were harvested by surgical team from the right sub-costal diaphragm after 72 hours of CMV and after the 2-hours of inadequate assisted ventilation period for each piglet. Samples of dissected diaphragm strips were immediately fixed for electron microscopy examination immersed in a solution of 2.5% glutaraldehyde in PHEM buffer (1X, pH 7.4) overnight at 4°C. Sections were then rinced in PHEM buffer and postfixed in a 0.5% osmic acid for 2 hours at dark and room temperature. After two rinces in PHEM buffer, the cells were dehydrated in a graded series of ethanol solutions (30-100%). The muscle was embedded in EmBed 812 using an Automated Microwave Tissue Processor for Electronic Microscopy, Leica EM AMW, Nanterre, France. Thin sections (70 nm with Leica-Reichert Ultracut E) were collected at different levels of each block. These sections were counterstained with uranyl acetate 1.5% in 70% ethanol and lead citrate.

The sections were observed using a Tecnai F20 transmission electron microscope (Colombus, USA) at 200KV equipped with a digital camera (Veleta, SIS, Olympus, Munster, Germany) in the Electronic Microscopy facilities, INM (Institut des Neurosciences de Montpellier), INSERM, Université de Montpellier, Montpellier France. Computer images captured from randomly selected microscopic fields were analyzed by two independent observers blinded to group allocation. A total of 12 micrographs per piglet were examined, 6 from diaphragm before inadequate assisted ventilation and 6 from diaphragm after inadequate assisted ventilation. The percentage of area including sarcomeric injuries was determined by a standardized stereology grid method (E7) using ImageJ® software. As described in previous study (E8), disrupted sarcomeres were defined as a zone with distinct distortion of the usual sarcomeric architecture.

Statistical Analysis

All statistical analyses were performed using R software 3.6.2 (R Project for Statistical Computing). All *p* values were two-tailed, and a *p* value of less than 0.05 was required to rule out the null hypothesis. After performing a Shapiro-Wilk test to ensure the normality of the variables distribution, we expressed data as mean ± SD. Comparison of two means was performed using a paired Student t-test. For diaphragm function assessment, comparison between groups and changes along stimulation frequency were performed by two-way ANOVA. Repeated measures analysis of variance and multiple paired t-test were applied for post hoc analysis with Bonferroni correction.

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SUPPLEMENTARY TABLES AND FIGURES

Table S1: ventilatory characteristics and respiratory mechanics under asynchronous intermittent mandatory ventilation.

Animal	Spont cycle rate (%)	RR (c/min)	Spont swing P_{es} (cmH_2O)*	E_{cw} (cmH_2O/L)	Spont P_{cw} (cmH_2O)*	Spont P_{mus} (cmH_2O)*	Spont Vt (mL)*	Mand Vt (mL)	Spont $P_{es}0.1$ (cmH_2O)*
Piglet 1	73	19	2.3 (±0.4)	8.0	0.9 (±0.1)	3.2 (±0.5)	111 (±13)	320	0.8 (±0.3)
Piglet 2	78	23	10.1 (±0.8)	10.7	1.4 (±0.1)	11.5 (±0.9)	132 (±11)	230	3.0 (±0.7)
Piglet 3	85	35	6.3 (±1.2)	7.6	0.6 (±0.1)	5.9 (±1.3)	83 (±9)	240	2.3 (±0.9)
Piglet 4	95	93	9.1 (±0.8)	15.8	0.5 (±0.1)	9.6 (±0.9)	34 (±5)	260	5.6 (±2.1)
Piglet 5	93	79	3.5 (±0.6)	15.5	0.4 (±0.1)	3.9 (±0.7)	28 (±8)	290	2.6 (±1.6)
Piglet 6	86	38	3.1 (±0.2)	4.3	0.3 (±0.1)	3.4 (±0.3)	80 (±4)	280	0.9 (±0.3)
Piglet 7	66	15	6.0 (±2.4)	4	0.6 (±0.1)	6.6 (±2.5)	159 (±23)	240	1.2 (±0.5)
Piglet 8	83	30	12.4 (±1.6)	11.5	1.8 (±0.2)	14.2 (±1.8)	161 (±21)	240	2.8 (±0.9)
Piglet 9	80	26	8.0 (±1)	12.5	1.2 (±0.2)	9.2 (±1.2)	97 (±14)	280	1.8 (±0.6)

**Data are presented as mean (±Standard Deviation)*

Abbreviations. Spont: spontaneous. RR: respiratory rate. P_{es}: esophageal pressure. E_{cw}: chest wall elastance. P_{cw}: chest wall recoil pressure. P_{mus}: muscular pressure. V_t: tidal volume. Mand: mandatory. $P_{es}0.1$: negative esophageal pressure generated during the first 100 msec of an occluded inspiration

Table S2: ventilatory characteristics and respiratory mechanics under pressure support ventilation with premature cycling.

Animal	Dys cycle rate (%)	RR (c/min)	Swing P_{es} (cmH_2O)*	E_{cw} (cmH_2O/L)	Dys P_{cw} (cmH_2O)*	Sync P_{cw} (cmH_2O)*	Dys P_{mus} (cmH_2O)*	Sync P_{mus} (cmH_2O)*	Dys Vt (mL)*	Sync Vt (mL)*	$P_{es}0.1$ (cmH_2O)*	PEEP (cmH_2O)	PS (cmH_2O)
Piglet 1	62	13	4.3 (±0.8)	8.0	1.4 (±0.1)	1.6 (±0.1)	5.7 (±0.9)	5.9 (±0.9)	173 (±13)	205 (±8)	0.8 (±0.3)	6	6
Piglet 2	57	22	10.7 (±0.8)	10.7	1.4 (±0.1)	1.7 (±0.1)	12.1 (±0.9)	12.4 (±0.9)	131 (±11)	161 (±9)	3.0 (±0.7)	6	6
Piglet 3	13	39	12.7 (±1.4)	7.6	1.3 (±0.2)	1.0 (±0.1)	14.0 (±1.6)	13.7 (±1.5)	144 (±21)	112 (±8)	2.3 (±0.9)	7	8
Piglet 4	15	56	12.2 (±1.4)	15.8	0.7 (±0.1)	0.7 (±0.1)	12.9 (±1.5)	12.9 (±1.5)	91 (±8)	91 (±5.5)	5.6 (±2.1)	10	12
Piglet 5	11	37	2.0 (±0.4)	15.5	2.9 (±1.3)	1.1 (±0.2)	4.9 (±1.7)	3.1 (±0.6)	187 (±84)	72 (±15)	2.6 (±1.6)	8	12
Piglet 6	0	46	2.8 (±0.2)	4.3	-	0.7 (±0.1)	-	3.5 (±0.3)	-	165 (±6)	0.9 (±0.3)	6	5
Piglet 7	9	21	15.5 (±1)	4	1.1 (±0.1)	1.1 (±0.1)	16.6 (±1.1)	16.6 (±1.1)	272 (±23)	282 (±9)	1.2 (±0.5)	8	8
Piglet 8	42	26	14.8 (±1.6)	11.5	2.4 (±0.5)	2.6 (±0.4)	17.2 (±2.1)	17.4 (±2)	210 (±44)	230 (±37)	2.8 (±0.9)	7	6
Piglet 9	30	35	9.7 (±1)	12.5	2.4 (±0.5)	2.7 (±0.5)	12.1 (±1.5)	13.3 (±1.2)	195 (±37)	220 (±36)	1.8 (±0.6)	8	8

**Data are presented as mean (±Standard Deviation)*

Abbreviations. Dys: dyssynchronous. RR: respiratory rate. P_{es}: esophageal pressure. E_{cw}: chest wall elastance. P_{cw}: chest wall recoil pressure. Sync: synchronous. P_{mus}: muscular pressure. V_t: tidal volume. $P_{es}0.1$: negative esophageal pressure generated during the first 100 msec of an occluded inspiration. PEEP: positive end expiratory pressure. PS: pressure support.

Table S3: individual values of hemodynamic and respiratory variables, and sedation dose, after 72 hours of totally controlled mechanical ventilation, before and after 2 additional hours of inadequate assisted ventilation.

	After 72hrs of totally controlled mechanical ventilation		
	Before 2hrs underassistance and dyssynchrony	**Before 2hrs underassistance and dyssynchrony**	***p-values****
Hemodynamic variables			
MAP (mmHg)	71 (±7)	72 (±15)	0.89
Heart rate (bpm)	82 (±29)	128 (±17)	< 0.01
Cardiac output (L/min)	3.77 (±0.93)	4.82(±1.37)	0.08
Norepinephrine (µg/kg/min)	0.35 (±0.63)	0.16(±0.49)	0.48
Lactate (mmol/L)	0.5 (±0.3)	2.2 (±4.1)	0.27
Respiratory variables			
Tidal volume (mL/kg)	9.2 (±1.1)	9.1 (±0.9)	0.82
Respiratory rate (c/min)	26 (±2)	26 (±1)	0.79
PEEP (cmH_2O)	6 (±1)	7 (±1)	0.37
Driving pressure (cmH_2O)	17 (±7)	19 (±7)	0.55
PaO_2/FiO_2 (mmHg)	262 (±84)	128 (±80)	< 0.01
$PaCO_2$ (mmHg)	48 (±11)	112 (±30)	< 0.01
pH	7.37 (±0.07)	7.06 (±0.09)	< 0.01
HCO_3 (mmol/L)	28 (±6)	31 (±3)	0.22
Sedation dose			
Propofol (mg/h)	99 (±30)	108 (±45)	0.62
Sufentanil (µg/h)	17 (±9)	13 (±8)	0.41
Midazolam (mg/h)	21 (±7)	18 (±3)	0.40
Ketamine (mg/h)	275 (±92)	245 (±38)	0.40

All data are presented as mean (±Standard Deviation)
**Student t-test*
Abbreviations. MAP: mean arterial pressure. PEEP: positive end expiratory pressure

Figure S1: diagram of preparation of the piglet model

PiCCO (Pulsion, Munich, Germany): pulse induced contour cardiac output

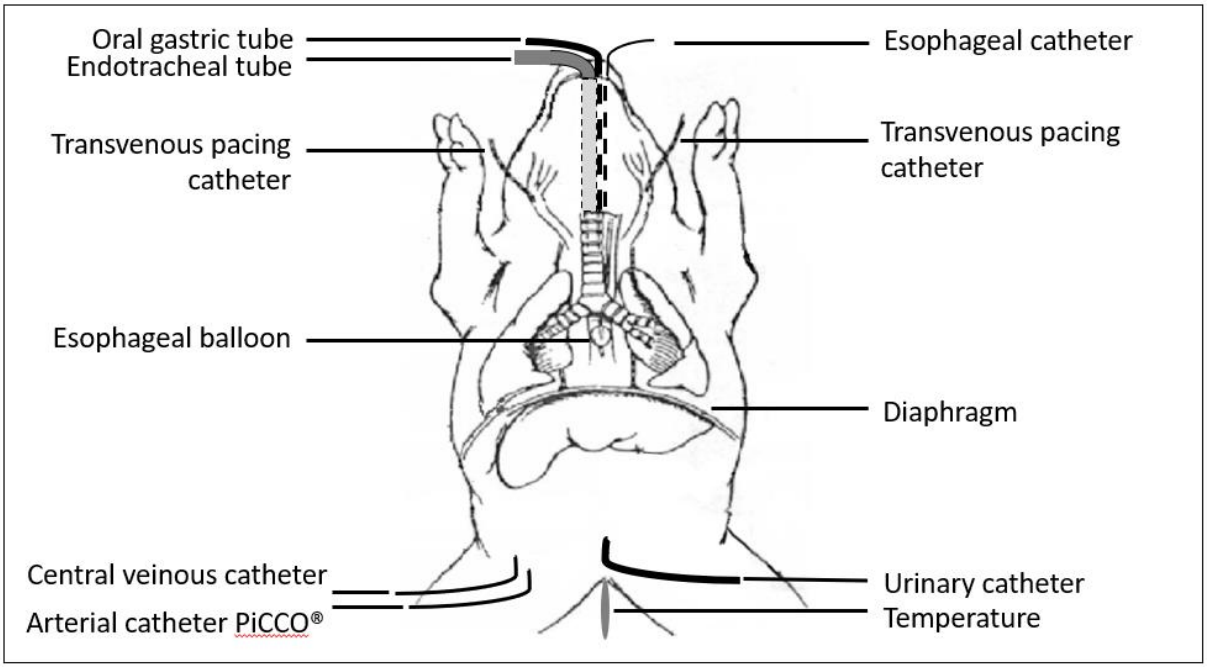
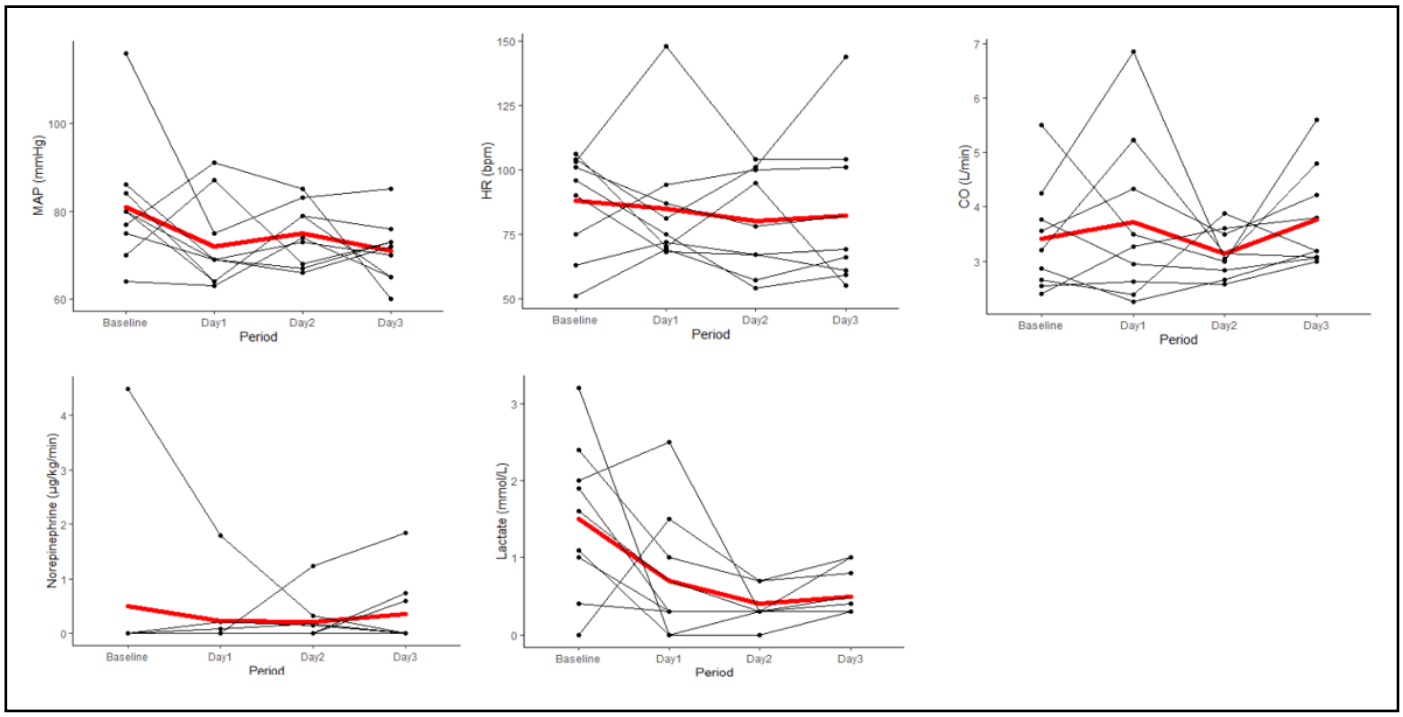


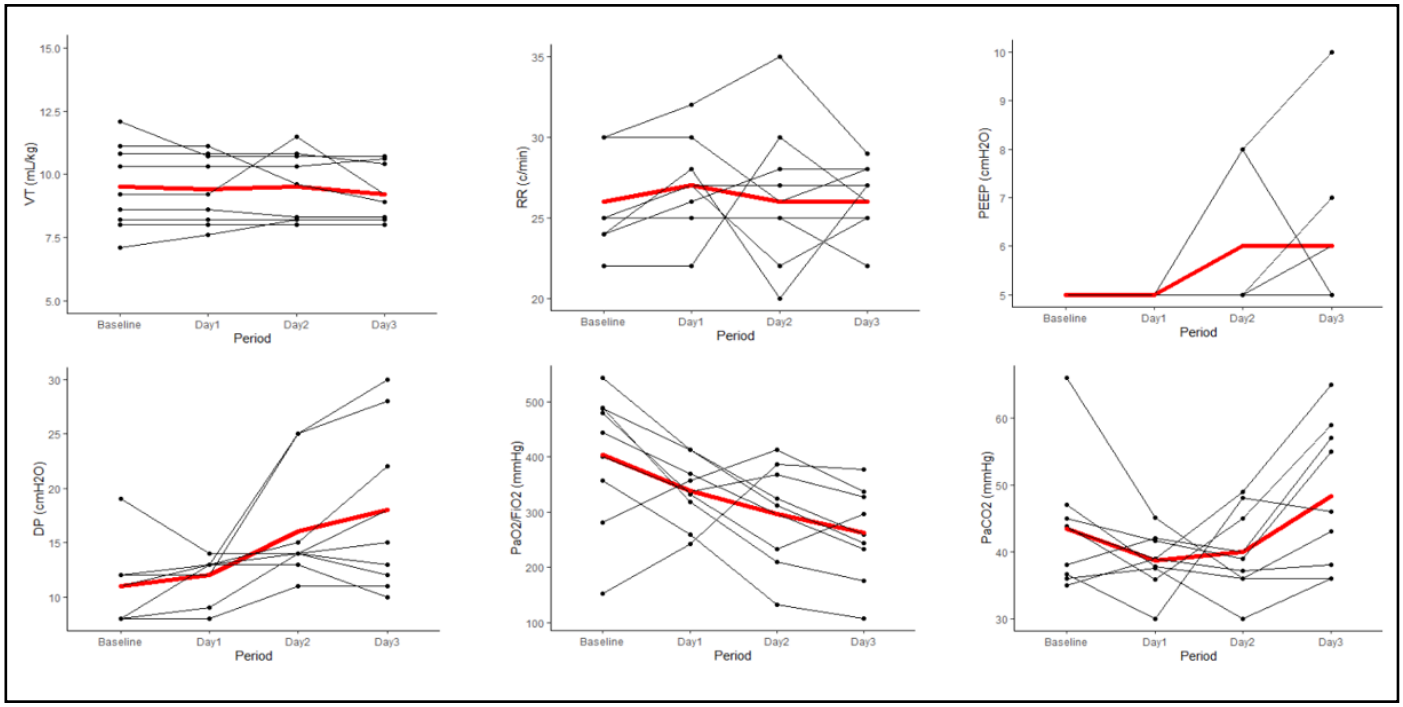
Figure S2: individual values of (A) hemodynamics variables, (B) respiratory variables, (C) metabolic variables and (D) sedation dose with average value (red line) at baseline, day 1, day 2 and day 3 of totally controlled mechanical ventilation.

MAP: mean arterial blood pressure. HR: heart rate. CO: cardiac output. VT: tidal volume. RR: respiratory rate. PEEP: positive end expiratory pressure. DP: driving pressure. FiO2: inspired fraction of oxygen.

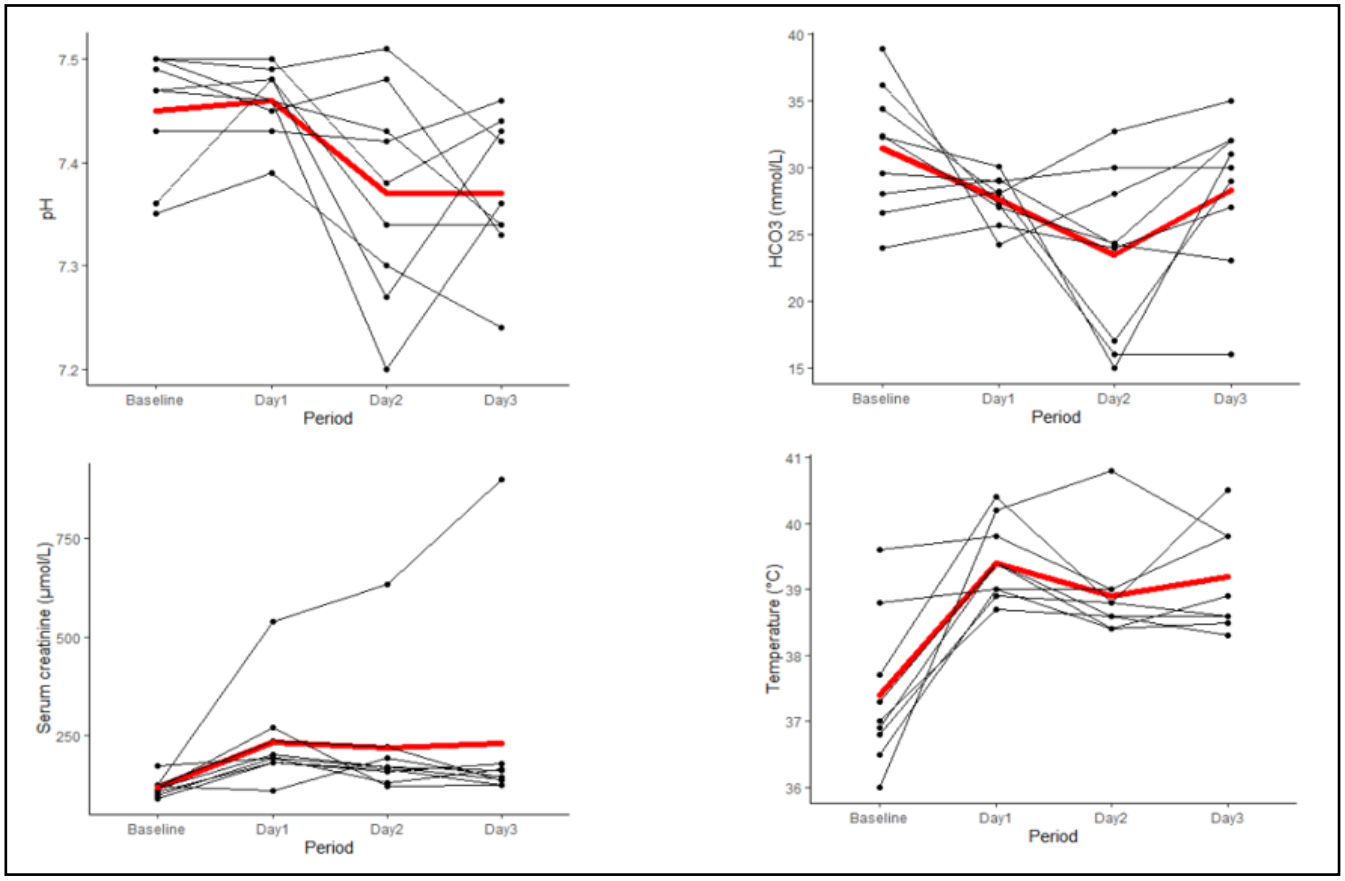
A



B



C


pH
7.5
7.4
7.3
7.2
Baseline
Day1
Day2
Day3
Period
HCO3 (mmol/L)
40
35
30
25
20
15
Baseline
Day1
Day2
Day3
Period
Serum creatinine (μmol/L)
750
500
250
Baseline
Day1
Day2
Day3
Period
Temperature (°C)
41
40
39
38
37
36
Baseline
Day1
Day2
Day3
Period

D

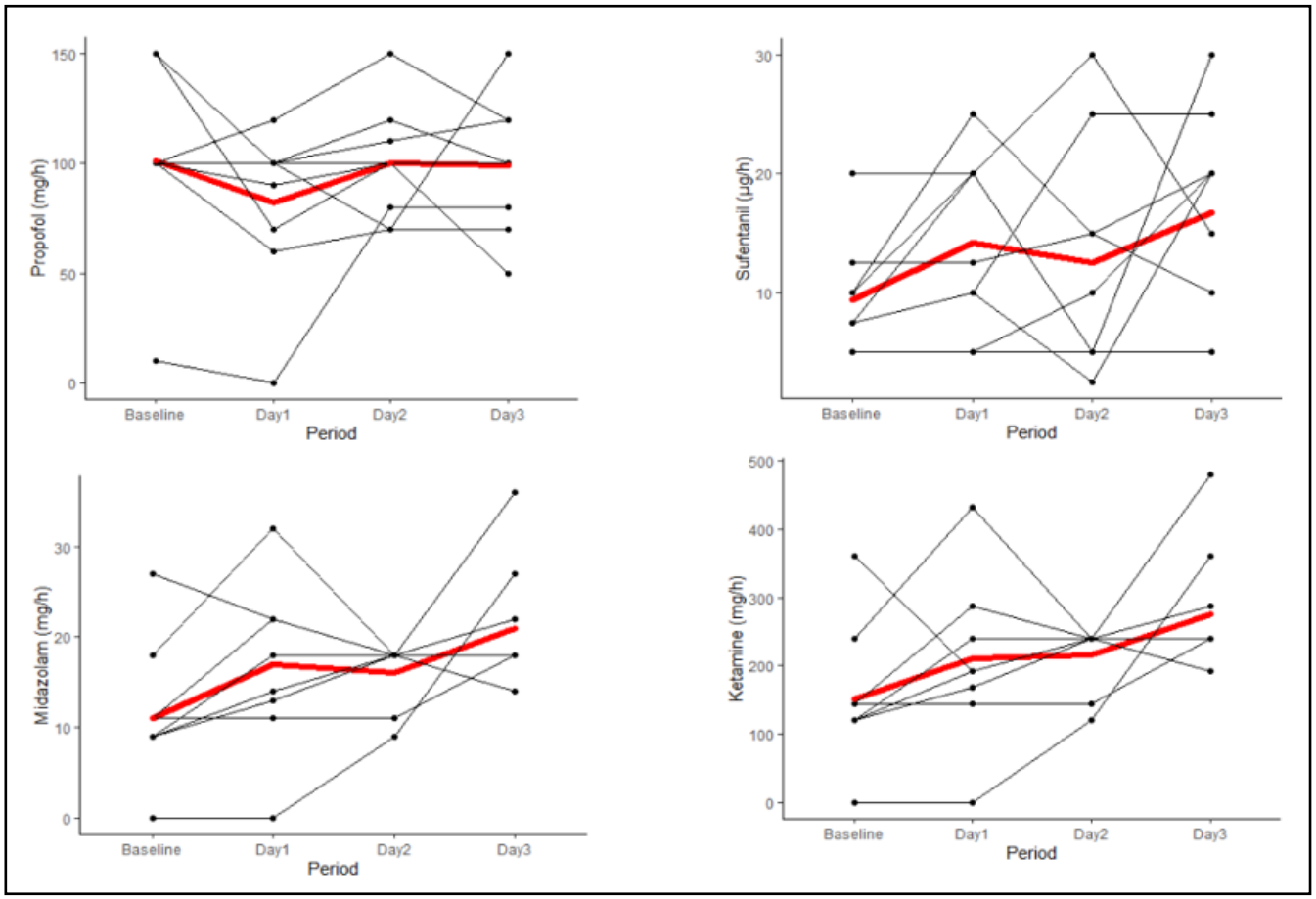

Propofol (mg/h)
150
100
50
0
Baseline
Day1
Day2
Day3
Period
Sufentanil (μg/h)
30
20
10
Baseline
Day1
Day2
Day3
Period
Midazolam (mg/h)
30
20
10
0
Baseline
Day1
Day2
Day3
Period
Ketamine (mg/h)
500
400
300
200
100
0
Baseline
Day1
Day2
Day3
Period

Figure S3: individual values of dyssynchrony rate (expressed in percentage of tidal respiratory cycles) and inspiratory efforts (esophageal pressure).

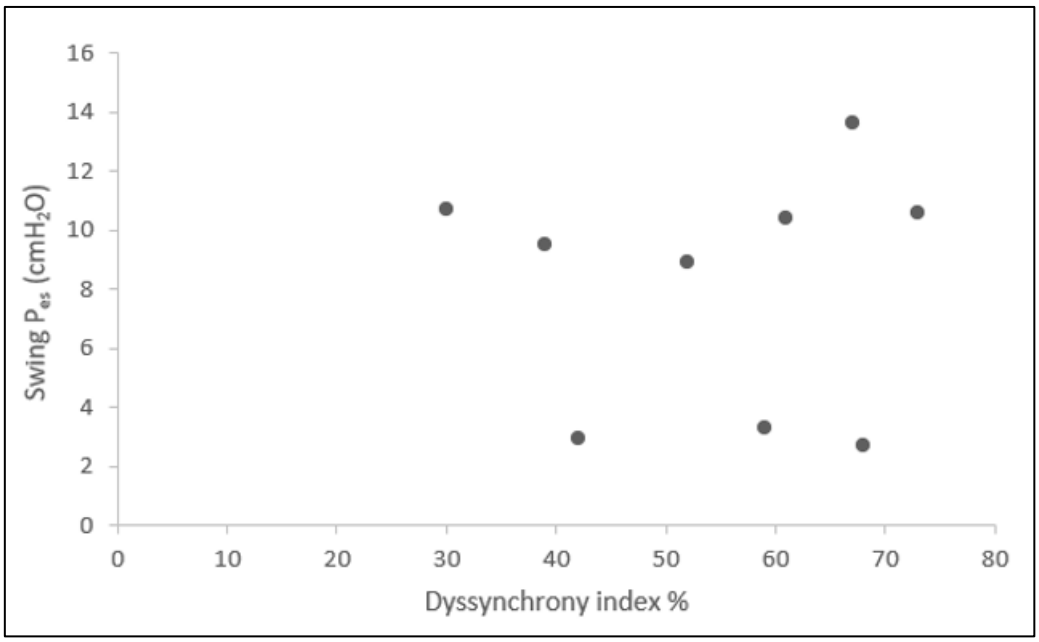


Figure S4: individual values of breathing effort represented by mean of swing esophageal pressure (P_{es}). Piglets were divided into three groups according to the level of breathing effort using mean swing P_{es} terciles.

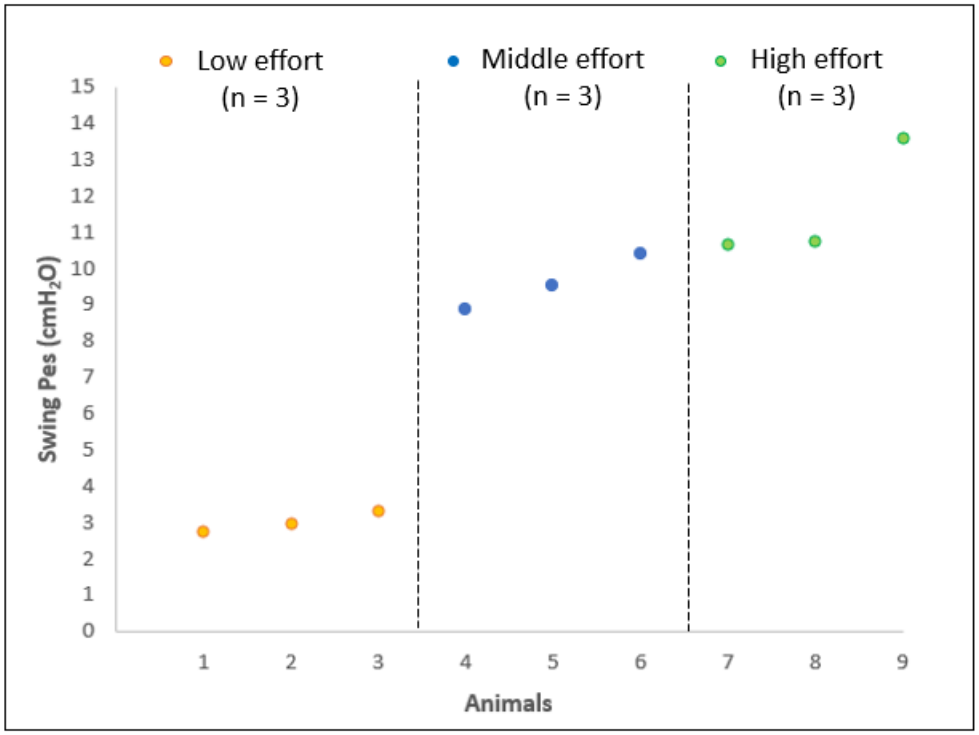
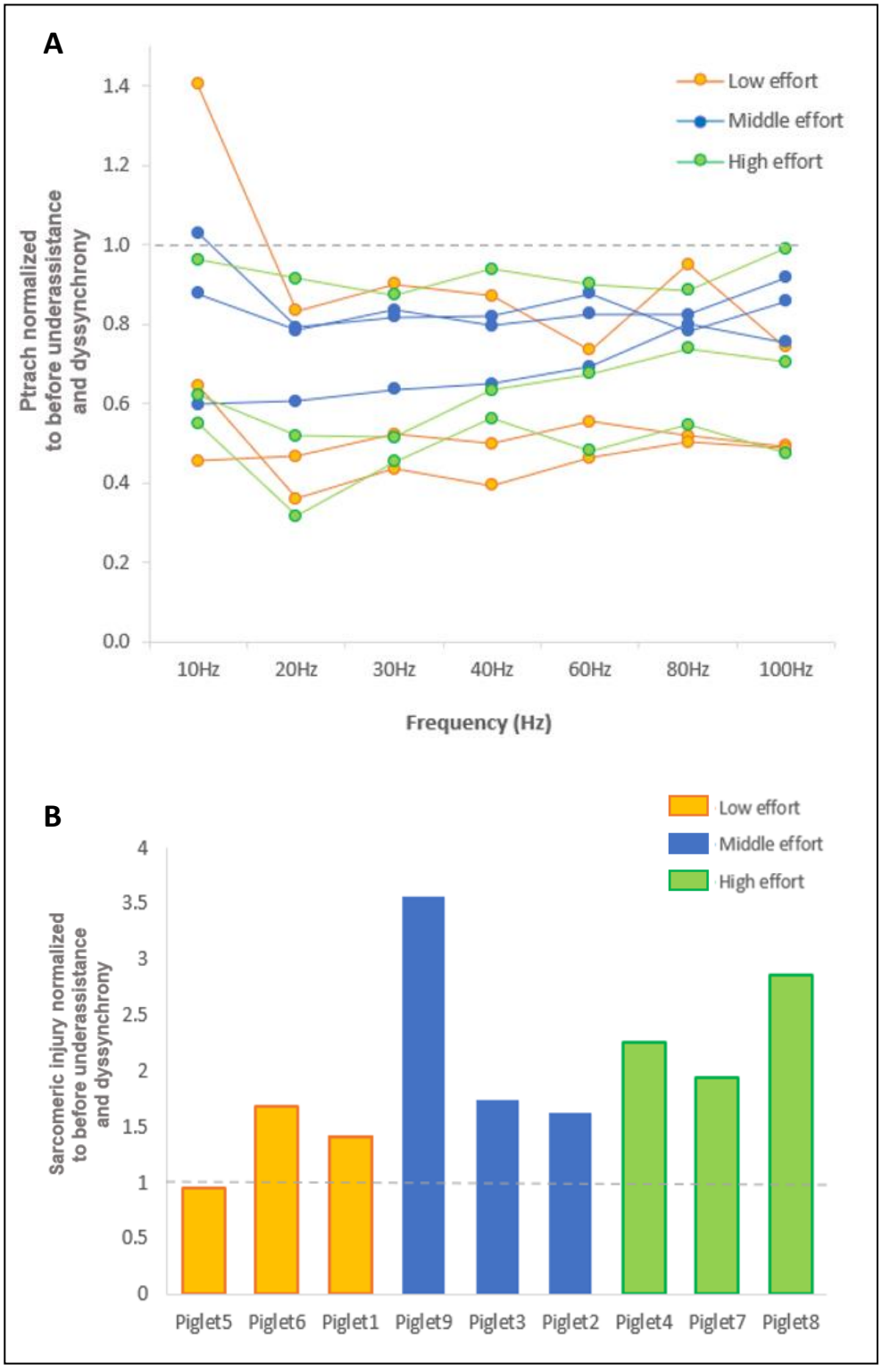


Figure S5: After 72 hours of totally controlled mechanical ventilation, ratio of individual values obtained after 2 additional hours of inadequate assisted ventilation over values before inadequate assisted ventilation of the same piglets. (A) Tracheal pressure (P_{trach}) after diaphragmatic stimulation at different frequencies (force frequency curves). (B) Percentage area of diaphragm sarcomeric injury. Dashed grey line represents no change in force / structure (P_{trach} or sarcomeric injury ratio of one). Piglets were divided into three groups according to the level of breathing effort.



Longitudinal diaphragm structure assessment from in vivo biopsies after inadequate assisted ventilation in a porcine model of short versus prolonged totally controlled mechanical ventilation

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Words count body manuscript n= 1008
References n= 9
Figures n=2

INTRODUCTION

Mechanical ventilation is a life-saving intervention and the main organ support in intensive care units (ICU). However, it is a two-edged sword. Inappropriate ventilator settings can induce ventilator-induced lung injury and ventilator-induced diaphragm dysfunction (VIDD) (1). After recovery from acute illness, reducing sedation and achieving patient-adapted ventilation is a challenging process, with a delicate balance between over-assistance and under-assistance (2). VIDD due to over-assistance myotrauma (insufficient muscle loading) is well documented (3–5). The impact of under-assistance myotrauma (excess muscle loading) and eccentric myotrauma (due to dyssynchrony) on diaphragm structure and function remains controversial and speculative (6,7). To our knowledge there is no study evaluating the impact of inadequate assisted ventilation with under-assisted mechanical ventilation and dyssynchrony on diaphragm structure after short versus prolonged IMV. We hypothesized that under-assisted mechanical ventilation and severe subject-ventilator dyssynchrony generates damage to the diaphragm structure, moreover in case of pre-existing VIDD due to prolonged passive IMV.

MATERIAL AND METHODS

We performed an experimental study with agreement of The Institutional (University of Montpellier, France) and the Regional (CEEA-LR-36) Ethics Committees for Animal Research and Care. The French Ministry of Agriculture (Paris, France) approved the study protocol (APAFIS #15866 2018070509081002 and APAFIS #23000 2019112614376164).

Twenty-two Large-White piglets (29±2 kg), 12 in the first group and 10 in the second group, were sedated to ensure proper anesthesia, adequate ventilation without dyssynchrony and stable hemodynamics. No neuromuscular blocking agent were used. In a first group, piglets were under totally controlled mechanical ventilation (CMV) for 2 hours versus 72 hours for the second group and then both were exposed to 2 hours of under-assisted mechanical ventilation and dyssynchrony. A minimally invasive diaphragm biopsy was harvested after 72 hours of

CMV in the second group, and after the additional 2 hours of under-assisted mechanical ventilation and dyssynchrony in both groups. At the end of the experiment, piglets were euthanized with barbiturate overdose.

During the 2 hours of underassistance and induced dyssynchrony, the ventilator was first set in asynchronous intermittent mandatory ventilation mode (without trigger) with gradual decrease of RR to the lowest tolerated by the piglets with a target of 5 per minute. To induce under-assistance myotrauma, there was no pressure support for spontaneous cycles. The other respiratory parameters such as VT or PEEP were not modified. As in clinical practice, the ventilator was then switched to pressure support mode. To induce eccentric myotrauma, a high expiratory trigger sensitivity value of 70% of peak inspiratory flow was set leading to premature cycling. The pressure support level was optimized to obtain a VT of 8-10 ml kg^{-1}. The PEEP was not modified. During the 2 hours of underassistance and induced dyssynchrony, we regularly alternated the two ventilatory modes.

Mini-invasive muscle biopsies were harvested by surgical team from the right sub-costal diaphragm. Samples of dissected diaphragm strips were immediately fixed for electron microscopy examination. The sections were observed using a Tecnai F20 transmission electron microscope (Colombus, USA) at 200KV equipped with a digital camera (Veleta, SIS, Olympus, Munster, Germany) in the Electronic Microscopy facilities, INM (Institut des Neurosciences de Montpellier), INSERM, Université de Montpellier, Montpellier France. Computer images captured from randomly selected microscopic fields were analyzed by two independent observers blinded to group allocation. A total of 6 micrographs per piglet were examined in the first group, 12 micrographs per piglet in the second group (6 from diaphragm before inadequate assisted ventilation and 6 from diaphragm after). The percentage of area including sarcomeric injuries and lipid droplets accumulation were determined by a standardized stereology grid method (8) using ImageJ® software.

RESULTS

Of all the piglets, initially healthy, one died in each group. A rate of unassisted and dyssynchronous respiratory cycles (over all cycles) ranging from 24% to 73% according to piglet was observed during the two hours. The inspiratory effort during this 5-minutes selected tracing varies from 2.7±0.4 cmH_2O to 17±2.4 cmH_2O per cycle according to piglet.

In the first group, after 2 hours of inadequate assisted ventilation, diaphragm sarcomeric injuries (**Figure 1A**) represented 17±16% of total area of the micrographs and lipids fraction volume (**Figure 1B**) 2.3±2.6%. In the second group, after 72 hours of CMV, diaphragm sarcomeric injuries represented 13±10% of total area of the micrographs and lipids fraction volume 14±8% (significant difference with the short ventilation and inadequate assisted ventilation $p<0.01$). The rate of sarcomeric injuries rose to 24±19% after 2 additional hours of inadequate assisted ventilation ($p=0.03$ versus short ventilation and inadequate assisted ventilation, $p<0.01$ versus prolonged CMV alone). The proportion of lipids fraction volume was 11±6.1% (significantly higher than versus short ventilation and inadequate assisted ventilation $p<0.01$, and significantly lower than prolonged CMV alone $p=0.03$) (**Figure 2**). The diaphragm samples were analyzed with excellent agreement between the two observers (intraclass correlation coefficient > 0.9).

DISCUSSION

Two hours of under-assisted mechanical ventilation and severe subject-ventilator dyssynchrony are associated with additional damage to the diaphragm structure with an increase of sarcomeric injuries in this experimental piglet model. Lipids fraction volume decreased after the two hours.

Our piglet model of prolonged CMV, with transvenous phrenic nerve stimulation for diaphragm function assessment, was developed in our previous experiments (4,5). This time we added a 2-hour period of under-assisted mechanical ventilation and severe dyssynchrony

after reducing sedation and using simple unsuitable respiratory parameters. Our aim was to amplify what could happen in clinical practice

Our study presents a limitation, we did not add groups without ventilation and with only short ventilation. We considered that short ventilation does not impair diaphragm structure as previously describe in a murine model.

This study provides additional data on the impact of the under-assistance and eccentric myotrauma induced by dyssynchrony, and arguments to encourage lung and diaphragm protective ventilation (9). After prolonged IMV, the switch to assisted ventilation should be made with caution, with adequate pressure support and parameters to avoid under assistance and dyssynchrony. In case of fast weaning process, the same precautions should be taken when performing a spontaneous breathing trial. To go further, we could investigate the impact of dyssynchrony in a piglet model of ARDS, sepsis, trauma, post operative status.

DECLARATIONS

ETHICS APPROVAL

The Institutional (University of Montpellier, France) and the Regional (CEEA-LR-36) Ethics Committees for Animal Research and Care, and the French Ministry of Agriculture (Paris, France) approved the study protocol (APAFIS #15866 2018070509081002).

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

Data are available from the corresponding author on reasonable request.

COMPETING INTERESTS

SJ reports receiving consulting fees from Drager, Mindray, Medtronic, Baxter, Fresenius-Xenios and Fisher & Paykel. ADJ reports receiving consulting fees from Drager, Medtronic and Fisher & Paykel. LB's lab has received research grants from Medtronic, Drager and Stimit and equipment from Sentec, Fisher & Paykel and Philips and lecture fees from Fisher & Paykel. No potential conflict of interest relevant to this article was reported for other authors.

FUNDING

Inserm Transfert (COPOC program).

AUTHOR'S CONTRIBUTIONS

MC and SJ designed the study. MC, JB, TL, YA, JP, LD, TS, AC and FR performed the intervention and acquired the data. MC, ADJ, NM and SJ contributed to data analysis. MC, BJ, JC, JYLG, FR, SM, LB AL and SJ were involved in data interpretation. MC, ADJ, JC and SJ drafted the manuscript and all authors reviewed it. All authors approved the final version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGMENTS

We thank all the teams of Department of Anesthesiology and Critical Care Medicine B (DAR B), Saint-Eloi Hospital. We thank all the teams of the laboratory PhyMedExp. We thank the surgical team of Saint-Eloi Hospital and especially Dr Bader Al Taweel. We would like to thank the technical platform of experimental research of Nimes (RAM-PTNIM) and Mrs Marylène Bacle for her precious help. We would like to thank the Institute of Neuroscience of Montpellier (INM) and Mrs Chantal Cazevieille for her help in electron microscopy examination.

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FIGURES

Figure 1: Representative electron microscopy images of longitudinal ultrathin sections obtained from the diaphragms showing (A) sarcomeric injury and (B) lipid droplets accumulation.

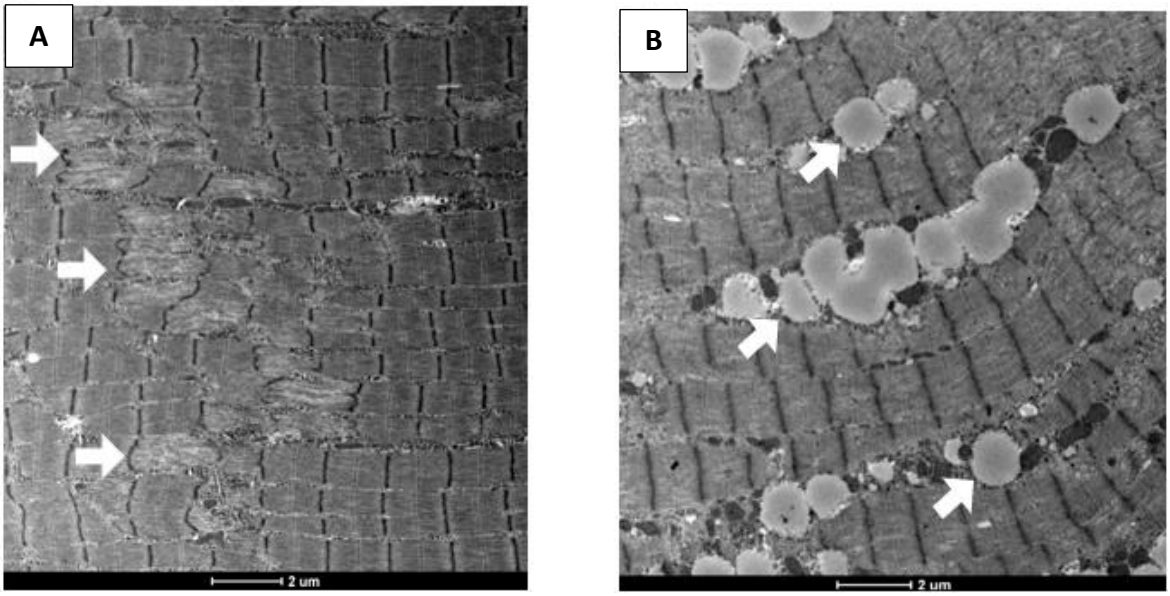
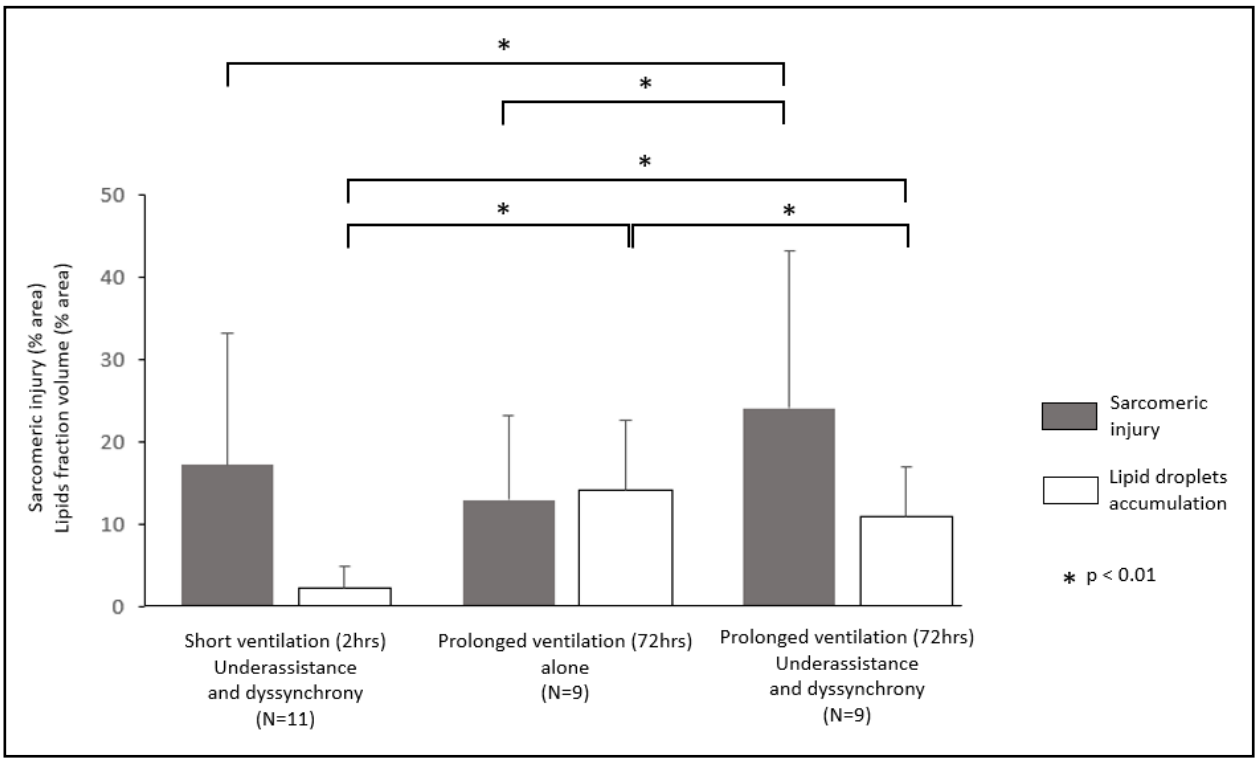


Figure 2: Structure assessment with percentage area of diaphragm sarcomeric injury and lipid droplets accumulation.



New method for bedside assessment of diaphragm function by phrenic nerve stimulation after ultrasound tracking

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Manuscript word count n = 1991
Words count abstract n = 270
References n = 21
Tables n = 2
Figures n = 3
Appendix n = 7

ABSTRACT

Background: Diaphragm dysfunction is common in intensive care unit and associated with weaning failure and mortality. Gold standard for the diagnosis is the transdiaphragmatic or tracheal pressure induced by magnetic phrenic nerve stimulation, but the equipment required is not commonly available and requires specific technical skills. We aimed to evaluate a new method called Sonostim for early stage and accurate bedside assessment of diaphragm function by targeted electrical phrenic nerve stimulation.

Methods: In this randomized cross-over study we compared a new method of electrical phrenic nerve stimulation using a common neuromuscular transmission monitor coupled with ultrasound nerve tracking, with the gold standard, in intensive care unit adult patients under mechanical ventilation with a Richmond-Agitation-Sedation-Scale score of -4 or -5. Each patient received the two methods of stimulation, in a randomized order. The primary outcome was the tracheal pressure (P_{trach}) induced by stimulation.

Results: One hundred sixteen patients were included and analyzed in whom 77 presented a diaphragm dysfunction (P_{trach} < 11 cmH2O) and 50 a severe diaphragm dysfunction (P_{trach} < 8 cmH2O). With a R-squared of 0.908 ($p<0.001$) and a Pearson's correlation of 0.799 ($p<0.001$), the Sonostim method presented an excellent correlation with the gold standard. The receiver operating curves showed an excellent performance for the diagnosis of diaphragm dysfunction and severe diaphragm dysfunction with respectively an area under curve of 0.90 (CI95 0.83-0.97) and 0.88 (CI95 0.82-0.95). This performance was not affected by the body mass index or the presence of a cervical catheter.

Conclusions: The Sonostim method is an easy to use and accurate tool for bedside assessment of diaphragm function with phrenic nerve stimulation after ultrasound tracking.

Keywords: diaphragmatic dysfunction, mechanical ventilation, phrenic nerve stimulation

BACKGROUND

Diaphragm dysfunction is common in ventilated intensive care unit (ICU) patients with an incidence from 53% at initiation of mechanical ventilation (MV),[1] 64% 24 hours after ICU admission[2] and up to 80% at 48 hours of MV.[3] Several causes of critical illness-associated diaphragm dysfunction are identified[4] such as sepsis, surgery, use of neuromuscular blocking agents and most of all invasive MV.[5-7] Diaphragm dysfunction is associated with weaning failure[5,8] and mortality.[1-3]

The gold standard for diaphragm function assessment is the measurement of transdiaphragmatic pressure (P_{di}) or negative tracheal pressure (P_{trach}) induced by magnetic phrenic nerve stimulation.[9] However, the equipment required for magnetic stimulation is not commonly available and requires specific technical skills. Other simple bedside methods could be used for estimating the diaphragm function but with some drawbacks. Diaphragm thickness evaluated by diaphragm ultrasound could be informative[10,11] but difficult to interpret without stiffness details.[12] Assessment of diaphragm excursion[13] and thickening fraction [14,15] could be useful but only in case of spontaneous breathing activity. The maximal inspiratory pressure (Pimax) performed with the ventilator is a relevant tool for estimating the patient's effort to breathe but it is not specific to diaphragm function.[16]

An alternative for specific diaphragm function assessment in patients without spontaneous breathing activity could be electrical phrenic nerve stimulation[9]. This method has been described as not so accurate without exact position of the phrenic nerve, using old devices, and difficult to perform. Advances in ultrasound technology now enable us to identify the phrenic nerve course in cervical portion.[17] In this study, we aimed to evaluate a new method for early stage and accurate bedside assessment of diaphragm function by targeted electrical phrenic nerve stimulation, using a common neuromuscular transmission monitor coupled with ultrasound nerve tracking.

METHODS

Study design

We conducted a randomized cross-over study comparing a new method of targeted electrical phrenic nerve stimulation coupled with ultrasound nerve tracking and the gold standard magnetic stimulation for bedside assessment of diaphragm function in ICU patients with no or minimal spontaneous breathing activity. The trial was approved by a central Ethics Committee (2019-A01096-51, Comité de Protection des Personnes Sud-Ouest et Outre Mer III, Bordeaux, France) according to French law. Written informed consent was required. This study was registered at http://www.clinicaltrials.gov with trial identification number NCT04199273. The manuscript respects the STARD checklist for reporting of studies of diagnostic accuracy.[18]

Participants

The trial was conducted in a medical and surgical ICU for a total of 20 beds, in France. All consecutive ICU adult patients under invasive MV with a Richmond Agitation-Sedation Scale (RASS) score of -4 or -5 were eligible for inclusion. Patients fulfilling one or more of the following criteria were not included: contraindication for magnetic stimulation (patients with pacemakers or other devices affected by electromagnetic fields), hemodynamic or respiratory instability with arterial partial oxygen pressure over inspired oxygen fraction (PaO2/FiO2) <200 mmHg and/or noradrenaline > 0,3 µg/kg/min, neuromuscular disease or recent use of neuromuscular blocking agents with a time of four (TOF) ratio below 4/4 90%, pregnant or breastfeeding woman and protected person or under curatorship. Covid-19 related acute respiratory distress syndrome patients were not included.

Procedure

Phrenic nerve tracking was performed using a CX50® ultrasound machine with a L12-3 high-frequency linear probe (Philips, Amsterdam, Holland). The ultrasound probe was positioned at cervical level on the latero-medial axis to obtain an axial cross-section. The probe was

translated cephalo-caudally until the ideal ultrasound image was obtained, defined by 4 landmarks: the common carotid artery medially, the brachial plexus laterally, the sternocleidomastoid muscle anteriorly and the anterior scalene muscle posteriorly. It is usually challenging to identify the phrenic nerve which appears at the upper part of the lateral border of the anterior scalene muscle and has a lateral-to-medial course on the surface of the anterior scalene muscle, deep to the prevertebral layer of cervical fascia. To ensure a position close to the phrenic nerve, even if it is not formally identified by ultrasound, the electrode was positioned at the level of the ideal ultrasound image, centered on the area defined laterally by the brachial plexus and medially by the common carotid artery (**Figure 1**). The position of the electrode was reported on a standardized grid (**Figure S1**) for a comparison with the conventional anatomical position usually described for electrical phrenic nerve stimulation (lateral border of the sternocleidomastoid muscle at the level of the cricoid cartilage).[9]

Before stimulation the patient was placed in a semi-recumbent position, with a positive end expiratory pressure (PEEP) of 0 cmH2O. The endotracheal tube was disconnected from the ventilator, a pressure sensor connected to a MP100® data acquisition interface (Biopac, Goleta, California, USA) was fitted and then after gentle chest compression, the system was occluded. The electrical phrenic nerve stimulation (Sonostim method) was performed using a Innervator 252® neuromuscular transmission monitor (Fisher and Paykel, Auckland, New Zealand). After connection to the bilateral electrodes (placed during ultrasound phrenic nerve tracking), the electrical phrenic nerve pacing was initiated with an intensity of 60 mA and a frequency of 1 Hz. A gentle pressure was applied on electrodes to obtain an optimal contact between the stimulating electrode and the nerve (**Figure S2 A**). The magnetic phrenic nerve stimulation (gold standard) was performed using a MagStim 200® stimulator (Duomed, Aartselaar, Belgium) with two coils placed bilaterally at the level of the seventh vertebral body (**Figure S2 B**), at an intensity of 100%.[19] The acquisition software was AcqKnowledge® (Biopac, Goleta, California, USA).

Experimental protocol

The experimental protocol with timeline is summarized in **figure S3**. After inclusion in the study, the ultrasound phrenic nerve tracking was performed. Then a randomization defined which method of stimulation was delivered first. Each patient, serving as their own control, received the two methods of stimulation. Each method of stimulation was performed three times consecutively, and the higher value was retained. A 15-minute washout period with baseline ventilation was respected between the two methods of stimulation. Hemodynamic and respiratory variables were recorded after randomization and at the end of the washout period.

Outcomes

The primary outcome was the absolute value of P_{trach} after phrenic nerve stimulation. The secondary outcome was the position of the electrode after ultrasound phrenic nerve tracking. Other outcomes were the pain assessment during stimulation using the behavioral pain scale (BPS) score, the hemodynamic (heart rate, systolic diastolic and mean pressures) and respiratory variables (oxygen saturation, inspired fraction of oxygen, respiratory rate, end tidal carbon dioxide, tidal volume and minute ventilation).

Statistical analysis

With an expected sensitivity of 0.95±0.15 and an expected specificity of 0.75±0.15, with a prevalence of 65%, a confidence level of 95% and an expected dropout rate of 10%, the sample size was 103 patients. We decided to include 120 patients.

The baseline characteristics of the overall population and of each group were described. Categorical variables were reported as frequencies and percentages and continuous variables were reported as means with SDs. The comparison between the two methods about BPS was performed using the paired Wilcoxon signed rank test. Relationships between electrical stimulation and magnetic stimulation were assessed with linear regression and Pearson's correlation. Receiver operating curves (ROC) were constructed to evaluate the performance

of the electrical stimulation for the diagnosis of diaphragm dysfunction and severe diaphragm dysfunction, with area under curve (AUC) obtained using bootstrapping with 2000 replications. Sensitivities, specificities, positive and negative predictive values, positive and negative likelihood ratios were calculated. A value below the 11 cmH_2O threshold of absolute P_{trach} defines the diaphragm dysfunction[9] and a 8 cmH_2O threshold could define severe diaphragm dysfunction with higher weaning failure[1,20] and mortality.[1-3]

All analyses were conducted by the medical statistical department of the Montpellier University Hospital using statistical software SAS, V.9.4 (SAS Institute; Cary, NC, USA), R, V.4.2.1 and MedCalc (MedCalc Software bvba). Statistical significance was defined as $p \leq 0.05$.

RESULTS

From October 2019 to August 2022, 2246 adult patients were admitted in ICU and 1422 were under invasive mechanical ventilation. We included and randomized 120 patients. Four consecutive were then excluded due to technical issue thus 116 patients were finally analyzed (**Figure S4**). Baseline characteristics of the patients were presented in **Table 1**. Seventy-seven patients (66% of the overall population) presented a diaphragm dysfunction, including 50 patients (43% of the overall population) with sever diaphragm dysfunction.

There was an excellent correlation between electrical and magnetic stimulation (**Figure 2**) with a R-squared of 0.908 ($p<0.001$) and a Pearson's correlation of 0.799 ($p<0.001$). The ROC curves (**Figure 3**) showed an excellent performance of the Sonostim method for the diagnosis of diaphragm dysfunction and severe diaphragm dysfunction with respectively an AUC of 0.90 (CI95 0.83-0.97) and 0.88 (CI95 0.82-0.95). All performance metrics of the Sonostim method for the diagnosis of diaphragm dysfunction and severe diaphragm dysfunction are presented in **Table 2**.

The position of the phrenic nerve was more median under the sternocleidomastoid muscle using ultrasound in comparison to the conventional anatomical position (**Figure S5**). The median±SD value of BPS score during stimulation was 3±1 with electrical stimulation and 3±0 with magnetic stimulation ($p<0.001$). There was no significant difference in hemodynamic and respiratory variables between baseline and the end of washout period (**Table S1**).

In patients with obesity (33 patients, with a body mass index from 30.1 to 55.1 kg/m²), the correlation between electrical and magnetic stimulation remains excellent (**Figure S6**) with a R-squared of 0.862 ($p<0.001$) and a Pearson's correlation of 0.774 ($p<0.001$). Eighty-eight (76%) patients presented at least one central veinous catheter or dialysis catheter in the cervical region, and 14 patients (12%) presented a catheter on each side.

DISCUSSION

This study presents the Sonostim method as an accurate and easy to use bedside assessment tool for diaphragm function in ICU patients with an excellent correlation with the gold standard. This method is not affected by the BMI of the patient or the presence of a cervical catheter.

Critical illness-associated diaphragm dysfunction is common[1-3] and could have an important impact on the prognosis of ICU patients.[1-3,5,8] To our knowledge, there is no effective curative treatment for diaphragmatic dysfunction, thus it is very important to prevent and detect the first signs at an early stage. The most important cause of diaphragm dysfunction is the prolonged or inadequate mechanical ventilation.[5-7] To prevent ventilator induced diaphragm dysfunction (VIDD), a lung and diaphragm protective ventilation strategy is required.[21] The main objectives are to maintain a minimal diaphragm activity avoiding excessive inspiratory efforts.

The Sonostim method requires no additional special equipment. We speculate that an ultrasound machine and a neuromuscular transmission monitor are present in all intensive care units. Moreover, this method permits an early detection of diaphragm dysfunction even before patients show the first spontaneous breathing activity. This study presents however some limitations. First, awake patients were not evaluated. We already have higher pain scores during electrical stimulation in sedated patients, so it seems difficult to perform this electrical stimulation in non-sedated patients. However, we could adapt and add systematic analgesics before stimulation. Second, we have to maintain a pressure on the cervical electrode during electrical stimulation to obtain an accurate measurement. This could add inter-operator variability, which was not assessed in this study. Third we used an additional specific monitor for the pressure assessment. Intensivists could use their ventilators with an expiratory hold during stimulation, after PEEP diminution to 0 cmH2O, to measure the negative pressure induced by phrenic nerve stimulation. Four, we assume the potential potentiation effect due to repetitive phrenic nerve stimulation in the electrical method.

This easy-to-use bedside method offers many advantages for promoting early assessment of diaphragmatic function. We need to assess the impact of its use in daily practice on the incidence of diaphragmatic dysfunction and on the prognosis of ICU patients.

CONCLUSION

The Sonostim method is an easy to use and accurate tool for bedside assessment of diaphragm function with phrenic nerve stimulation after ultrasound tracking. The impact of its use in daily practice on the prognosis of ICU patients needs to be proven.

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Table 1. Baseline characteristics of the participants, the day of inclusion

	Overall (n=116)	Diaphragm dysfunction (n=77)		No diaphragm dysfunction (n=39)
		Overall (n=77)	Severe (n=50)	
Age, years	61±13	64±11	64±12	56±15
Male sex	77 (66%)	52 (68%)	37 (74%)	25 (64%)
BMI at admission, kg/m²	27±7	27±7	27±7	27±8
SAPS II at admission	54±20	58±19	58±19	45±19
SOFA score at admission	9±4	9±4	9±4	8±4
Comorbidities				
Alcohol abuse	50 (43%)	35 (45%)	24 (48%)	15 (38%)
Active smoking	41 (35%)	30 (39%)	21 (42%)	11 (28%)
Psychotropic treatment	39 (34%)	25 (32%)	17 (34%)	14 (36%)
Obesity with BMI > 30	33 (28%)	22 (29%)	15 (30%)	11 (28%)
Diabetes	28 (24%)	21 (27%)	16 (32%)	7 (18%)
Systemic hypertension	50 (43%)	38 (49%)	27 (54%)	12 (31%)
Coronary disease	24 (21%)	20 (26%)	15 (30%)	4 (10%)
Cardiac insufficiency	9 (7.8%)	8 (10%)	4 (8.0%)	1 (2.6%)
Chronic renal failure	16 (14%)	11 (14%)	6 (12%)	5 (13%)
Cirrhosis	43 (37%)	29 (38%)	18 (36%)	14 (36%)
Chronic respiratory failure	1 (0.9%)	0 (0%)	0 (0%)	1 (2.6%)
COPD	23 (20%)	18 (23%)	16 (32%)	5 (13%)
Immunocompromised	22 (19%)	15 (19%)	11 (22%)	7 (18%)
Main reason for ICU admission				
Post operative	39 (34%)	26 (34%)	20 (40%)	13 (33%)
Cardiac arrest	8 (6.9%)	7 (9.1%)	3 (6.0%)	1 (2.6%)
Sepsis	12 (10%)	9 (12%)	6 (12%)	3 (7.7%)
Coma	11 (9.5%)	6 (7.8%)	2 (4.0%)	5 (13%)
Acute respiratory failure	11 (9.5%)	8 (10%)	7 (14%)	3 (7.7%)
Acute kidney injury	1 (0.9%)	1 (1.3%)	1 (2.0%)	0 (0%)
ALF or ACLF	14 (12%)	11 (14%)	5 (10%)	3 (7.7%)
Massive hemorrhage	20 (17%)	9 (12%)	6 (12%)	11 (28%)
Main reason for intubation				
Before procedure*	59 (51%)	35 (45%)	26 (52%)	24 (61%)
Cardiac arrest	8 (6.9%)	7 (9.1%)	3 (6.0%)	1 (2%)
Shock	20 (17%)	16 (21%)	10 (20%)	5 (13%)
Coma	18 (15%)	11 (14%)	4 (8.0)	6 (15%)
Acute respiratory failure	11 (9.5%)	8 (10%)	7 (14%)	3 (8%)
Invasive mechanical ventilation duration, days	3±3	3±4	3±4	2±2
Use of sedation	113 (94%)	73 (92%)	48 (96%)	40 (98%)
Use of NMBA in the last 24 hours	46 (38%)	21 (51%)	20 (40%)	25 (32%)
Use of vasopressors	57 (48%)	39 (49%)	24 (48%)	18 (44%)

Data are presented in n (%) and mean±SD. BMI=Body Mass Index. SAPS=Simplified Acute Physiologic Score. SOFA=Sequential Organ Failure Assessment. COPD=chronic obstructive pulmonary disease. ICU=Intensive Care Unit. ALF=Acute Liver Failure. ACLF=Acute on Chronic Liver Failure. NMBA=Neuromuscular blocking agent. *Before procedure denoted that patients were intubated for a procedure, surgical or endoscopic.

Table 2. Performance metrics of the Sonostim method for the diagnosis of diaphragm dysfunction and severe diaphragm dysfunction.

	Diaphragm dysfunction	Severe diaphragm dysfunction
Threshold (cmH_2O)	11	8
AUC-ROC (CI95)	0.90 (0.83-0.97)	0.88 (0.82-0.95)
Sensitivity % (CI95)	95 (87-98)	94 (83-99)
Specificity % (CI95)	69 (56-83)	74 (62-84)
Likelihood ratio (CI95)		
Positive	3.08 (1.92-4.95)	3.65 (2.41-5.53)
Negative	0.08 (0.03-0.20)	0.08 (0.03-0.24)
Predictive values % (CI95)		
Positive	86 (79-91)	73 (65-81)
Negative	87 (72-95)	94 (84-98)

AUC= area under curve. ROC= receiver operating characteristics. CI95= 95% confidence interval.

FIGURE LEGEND

Figure 1: (A) Ultrasound image, (B) with anatomical structures highlighted, and (C) probe positioning.

The ultrasound probe was positioned at cervical level (C) on the latero-medial axis to obtain an axial cross-section. The ideal ultrasound image (A) was defined by 4 landmarks: the common carotid artery medially, the brachial plexus laterally, the sternocleidomastoid muscle anteriorly and the anterior scalene muscle posteriorly. The electrode was positioned (B) at the level of the ideal ultrasound image, centered on the area defined laterally by the brachial plexus and medially by the common carotid artery.

Figure 2: (A) Correlation between electrical stimulation using Sonostim method and magnetic stimulation, with (B) Blant-Altman plot.

(A) End-expiratory occlusion tracheal pressure in response to bilateral Sonostim method stimulation (y-axis) and Magnetic stimulation (x-axis). (B) Bland-Altman plot of agreement of end-expiratory occlusion tracheal pressure in response to bilateral Sonostim method stimulation and Magnetic stimulation. Each point representing an individual patient (n=116). Ptrach= tracheal pressure. SD= standard deviation.

Figure 3: Receiver operating characteristics curves of the Sonostim method for the diagnosis of diaphragm dysfunction and severe diaphragm dysfunction.

End-expiratory occlusion tracheal pressure in response to bilateral Sonostim method phrenic nerve stimulation for the diagnosis of diaphragm dysfunction and severe diaphragm dysfunction. AUC= area under curve.

Figure 1: (A) Ultrasound image, (B) with anatomical structures highlighted, and (C) probe positioning.

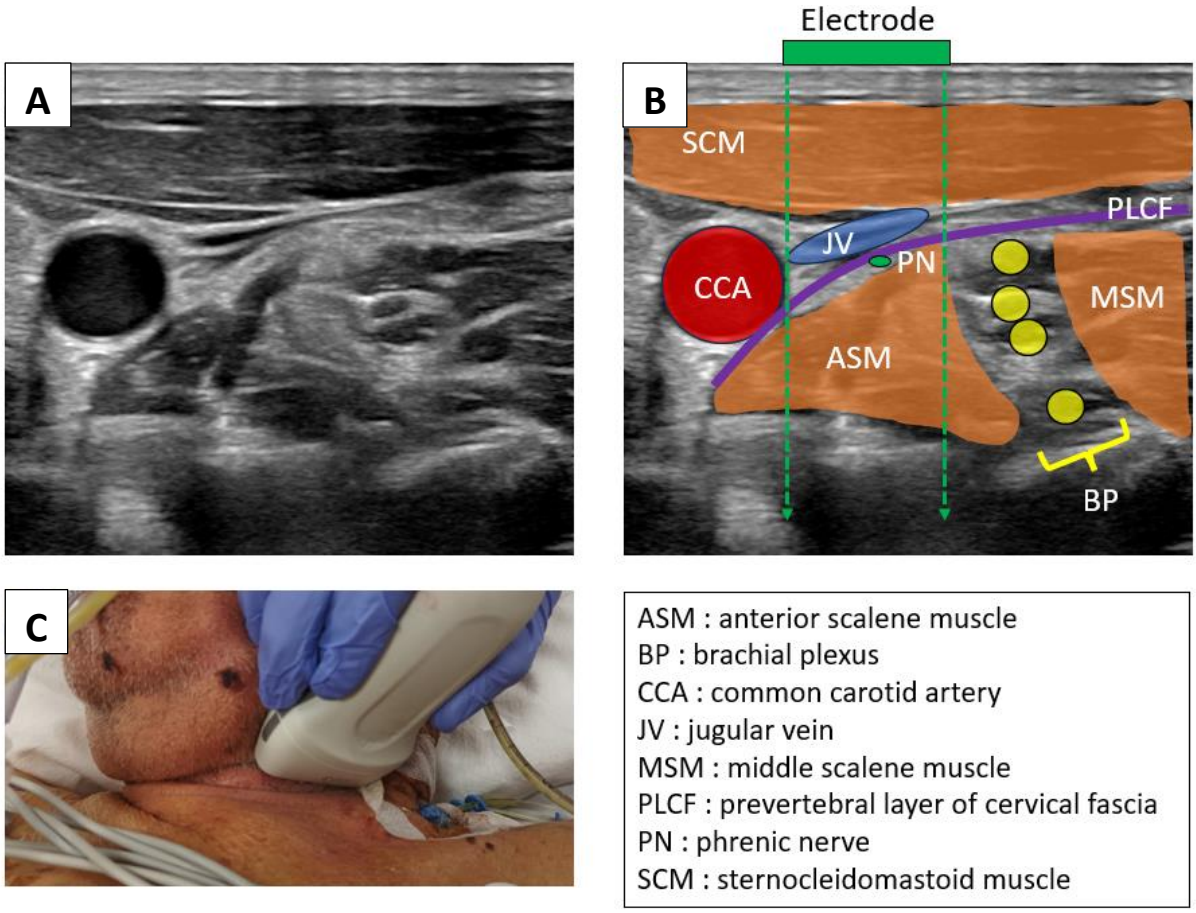
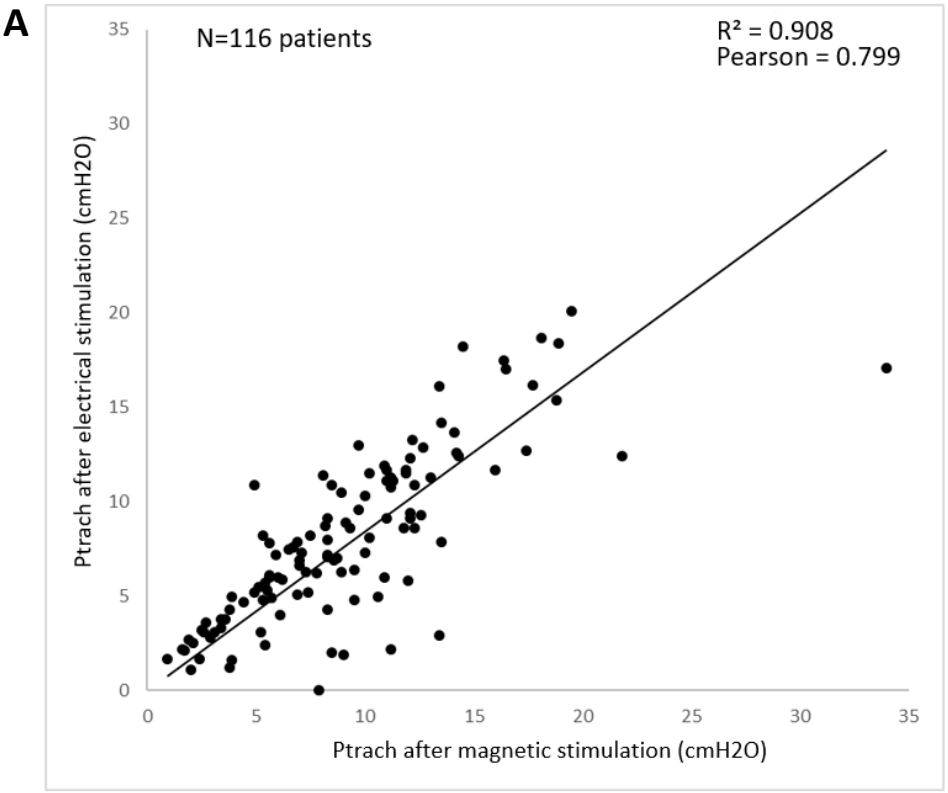


Figure 2: (A) Correlation between electrical stimulation using Sonostim method and magnetic stimulation, with (B) Blant-Altman plot.



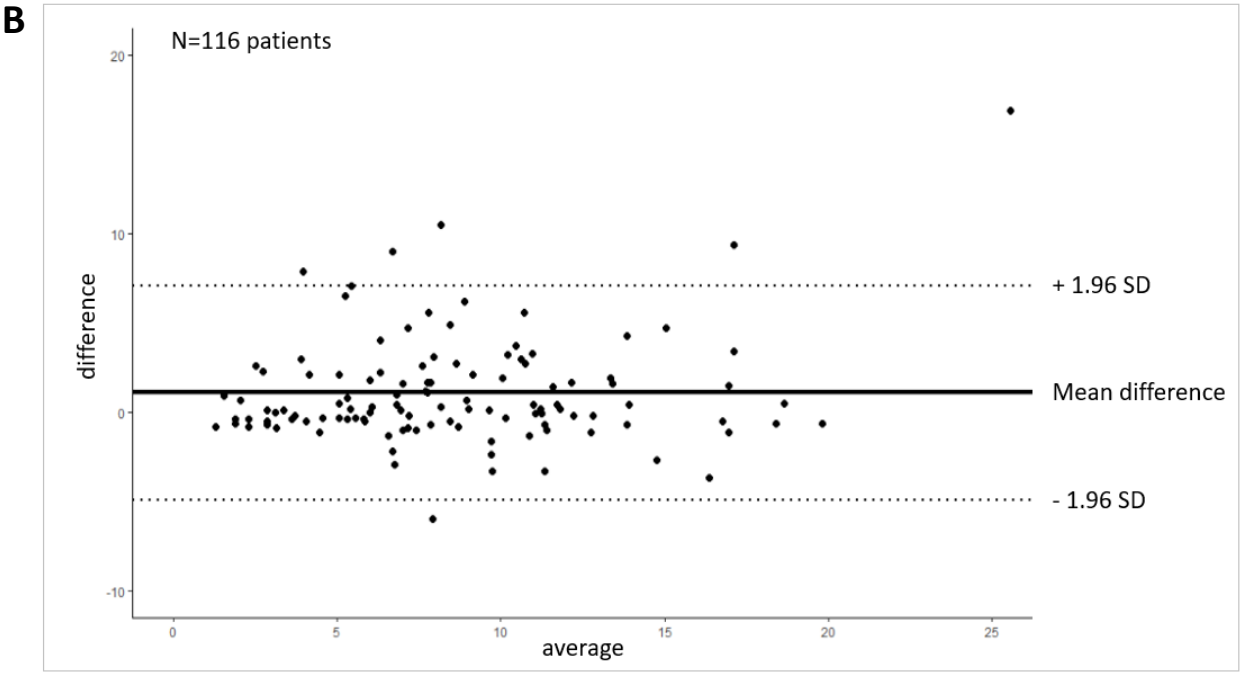
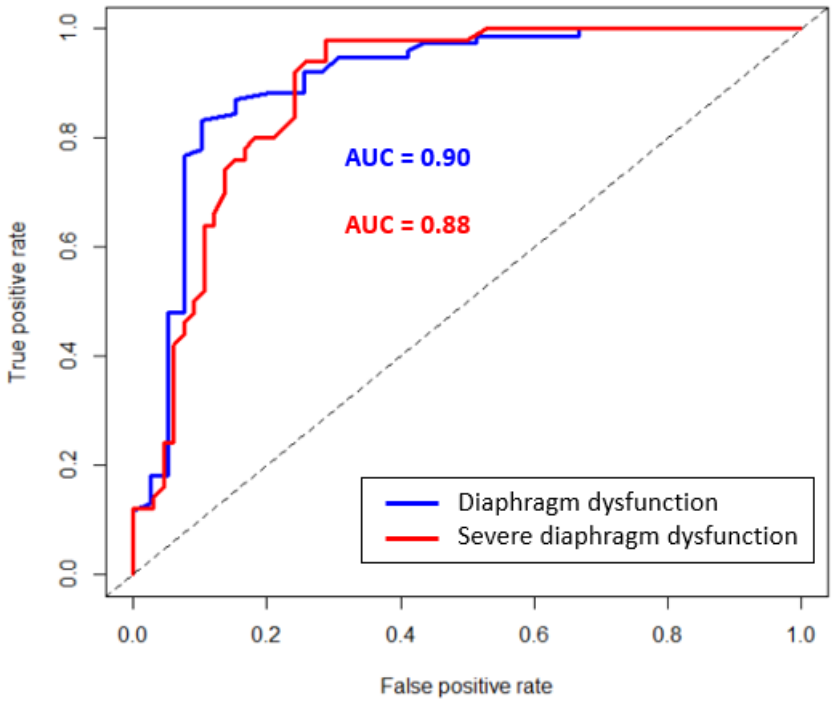


Figure 3: Receiver operating characteristics curves of the Sonostim method for the diagnosis of diaphragm dysfunction and severe diaphragm dysfunction.



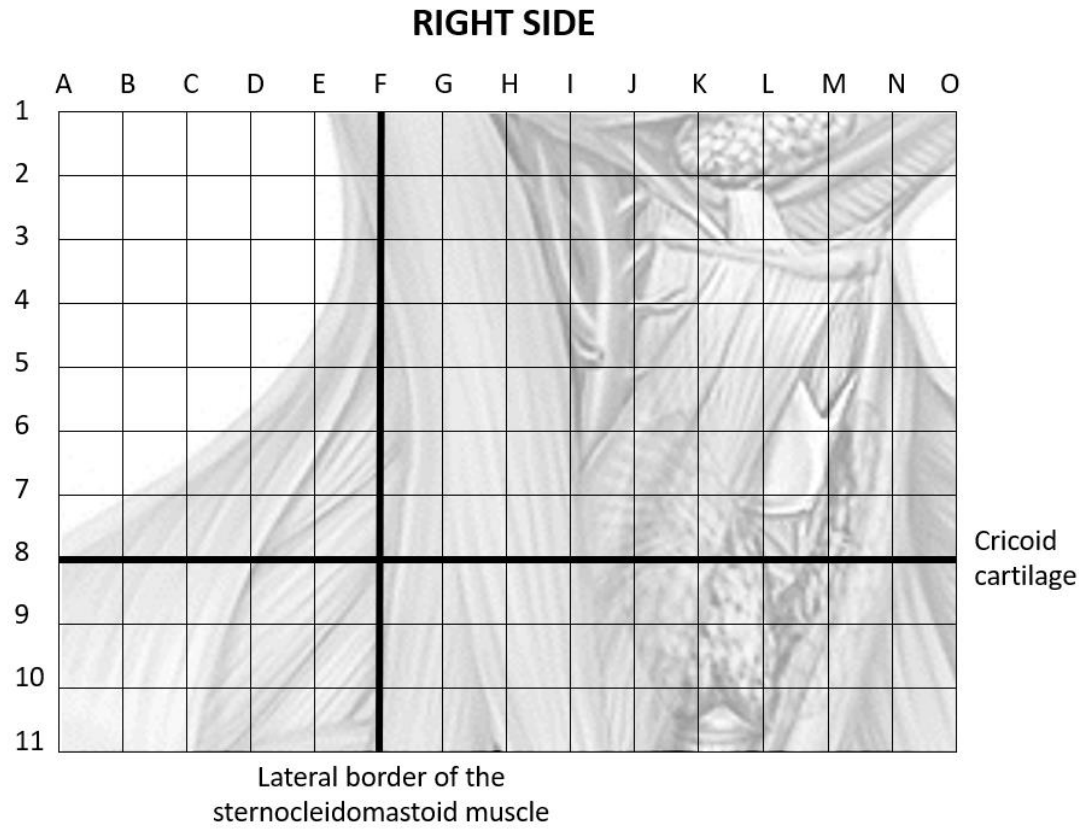
SUPPLEMENTARY APPENDIX

Table S1. Respiratory and hemodynamic variables at baseline, and at the end of the washout period just before the second stimulation.

	Baseline	Washout
SpO_2, %	98±2	98±2
FiO_2, %	34±7	35±7
RR, breaths/min	22±3	22±3
$EtCO_2$, mmHg	31±7	31±8
V_T, mL	404±60	407±59
RR/V_T, min/mL	55±12	54±11
V_E, L/min	9±9	9±9
HR, beats/min	82±20	81±20
SBP, mmHg	116±19	114±18
DBP, mmHg	59±9	58±9
MBP, mmHg	79±12	78±12

Data are presented in mean±SD. There was no significant difference in any variable between the two periods. SpO_2=Pulse oximetry. FiO_2=Inspired fraction of oxygen. RR=Respiratory Rate. $EtCO_2$=End tidal carbon dioxide. V_T=Tidal volume. V_E=Minute ventilation. HR=Heart Rate. SBP=Systolic Blood Pressure. DBP=Diastolic Blood Pressure. MBP=Mean Blood Pressure.

Figure S1: Standardized grid for electrode position.



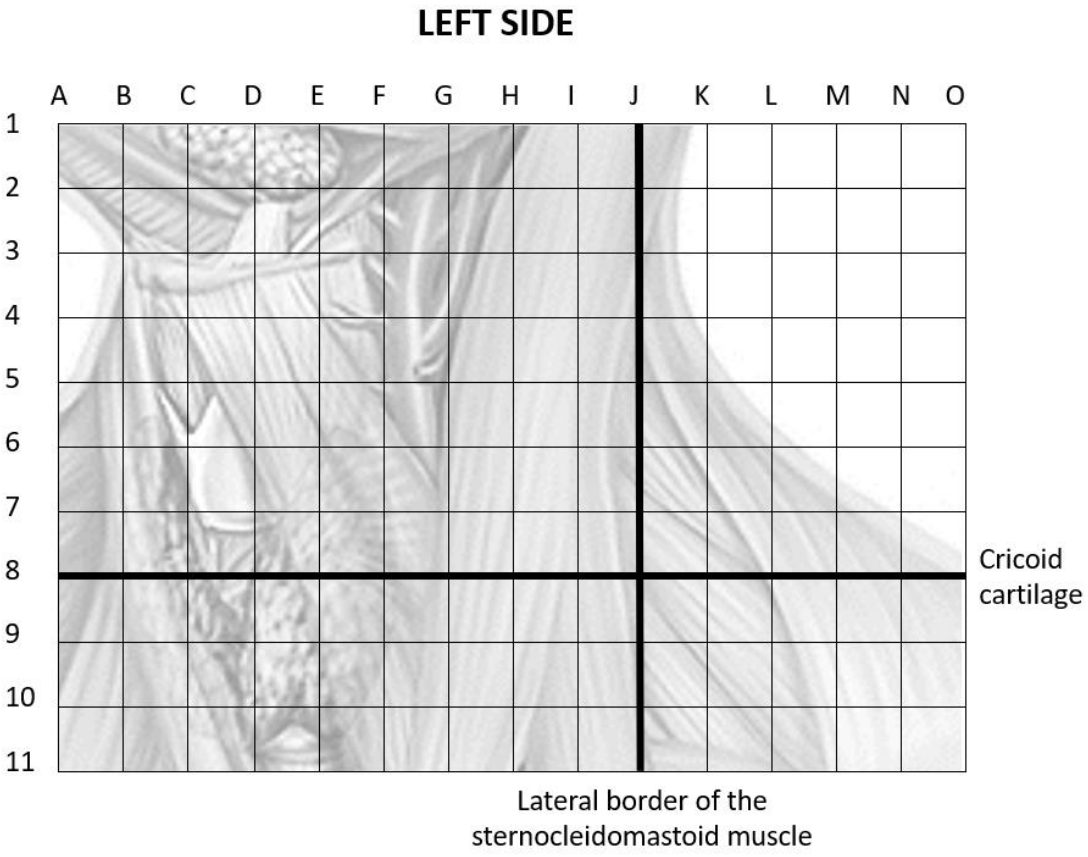


Figure S2: (A) Electrical and (B) magnetic stimulation with tracheal pressure curves.

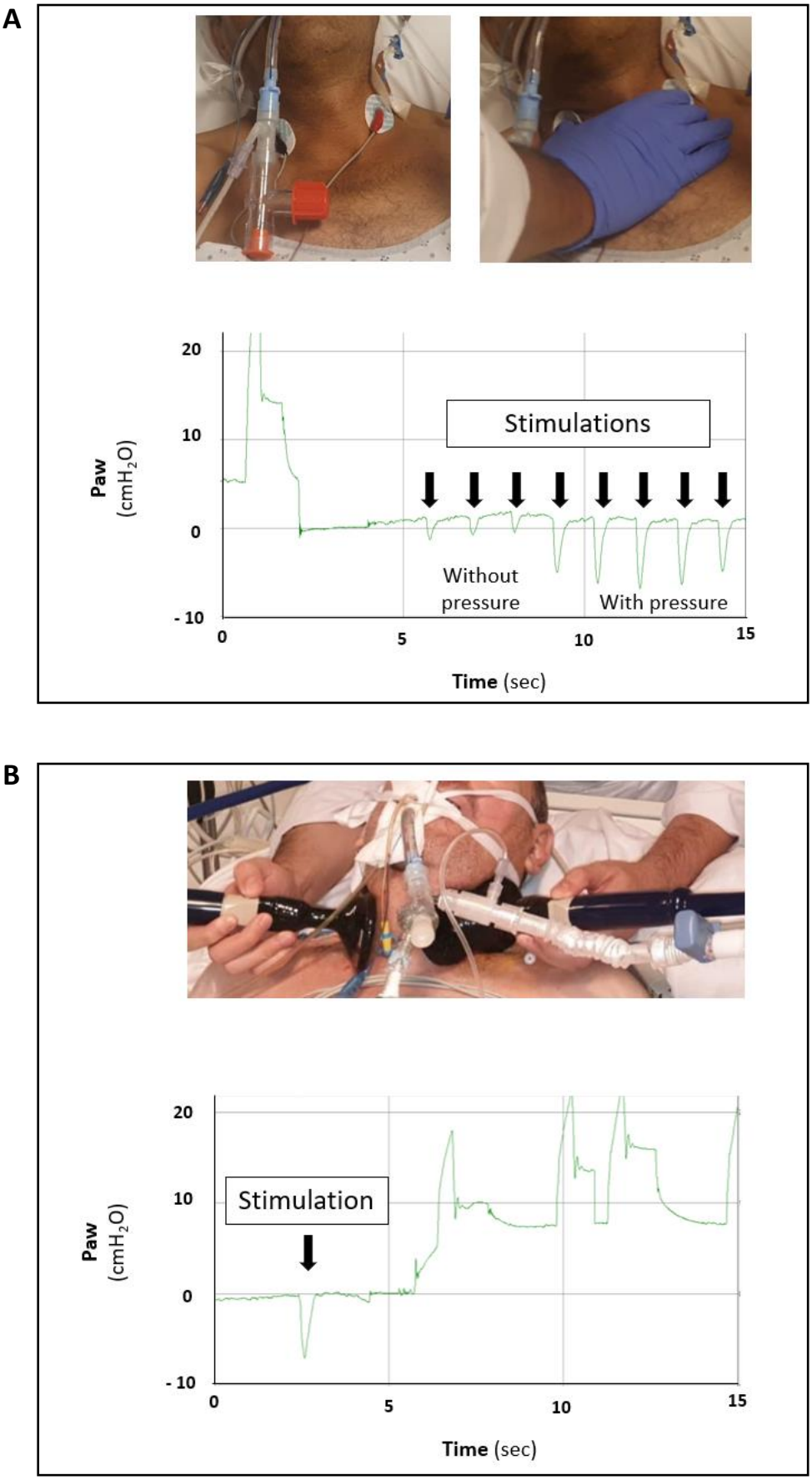


Figure S3: Experimental protocol.

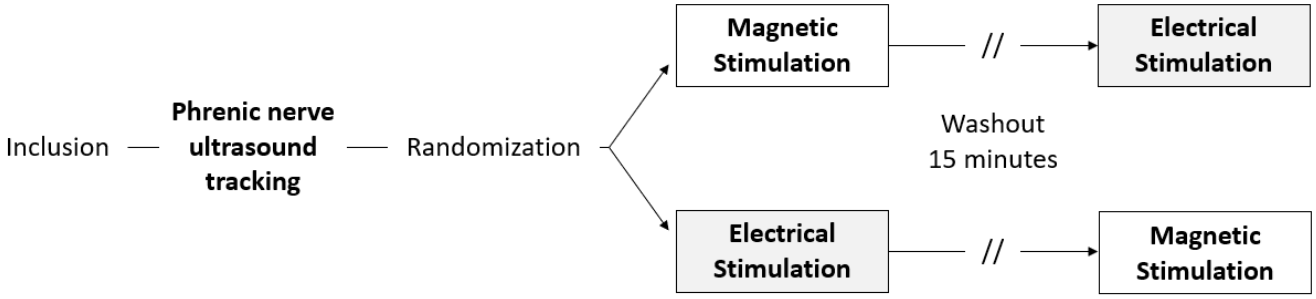


Figure S4: Flow chart.

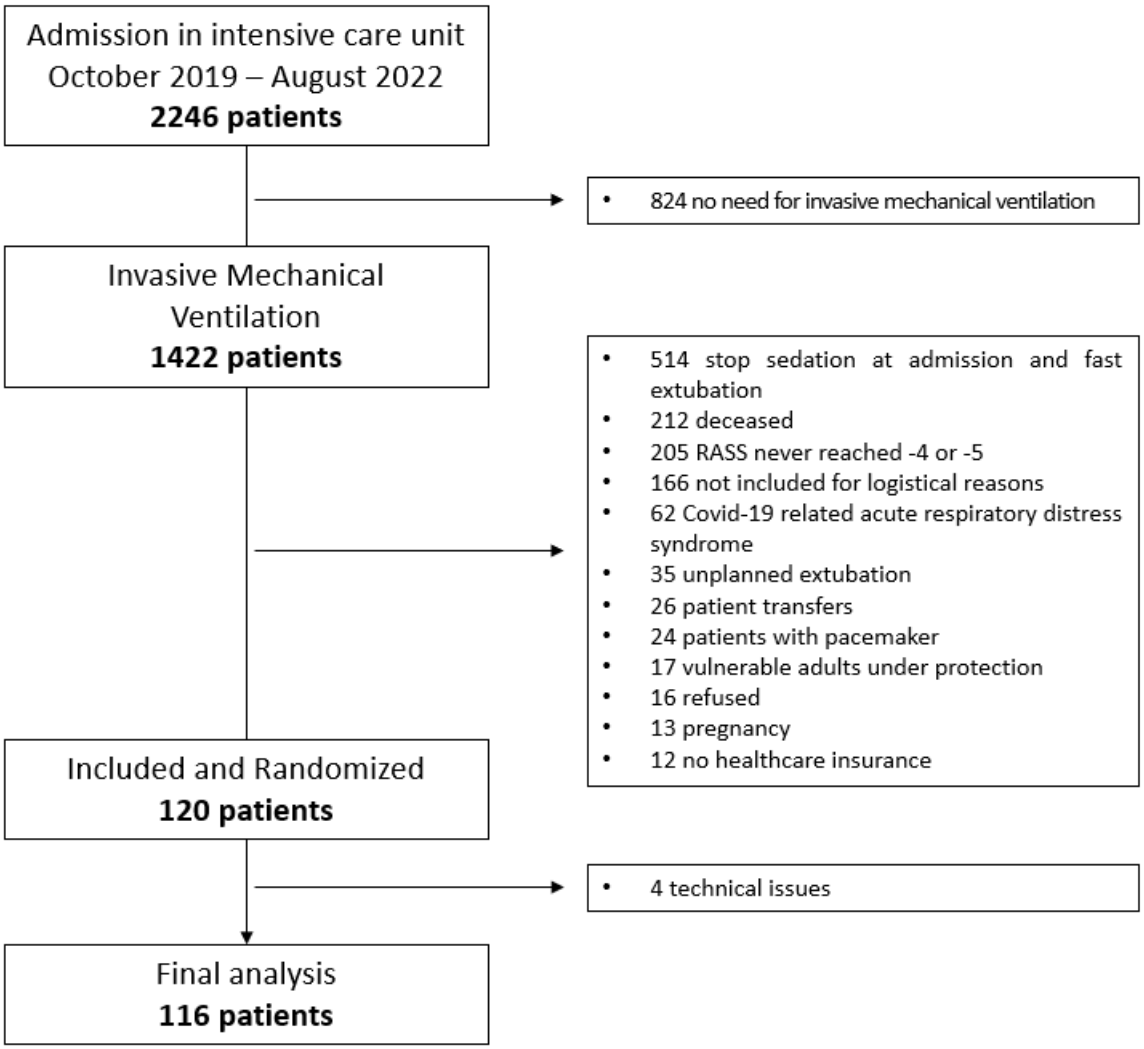


Figure S5: Electrode position after ultrasound tracking in comparison with conventional anatomical position.

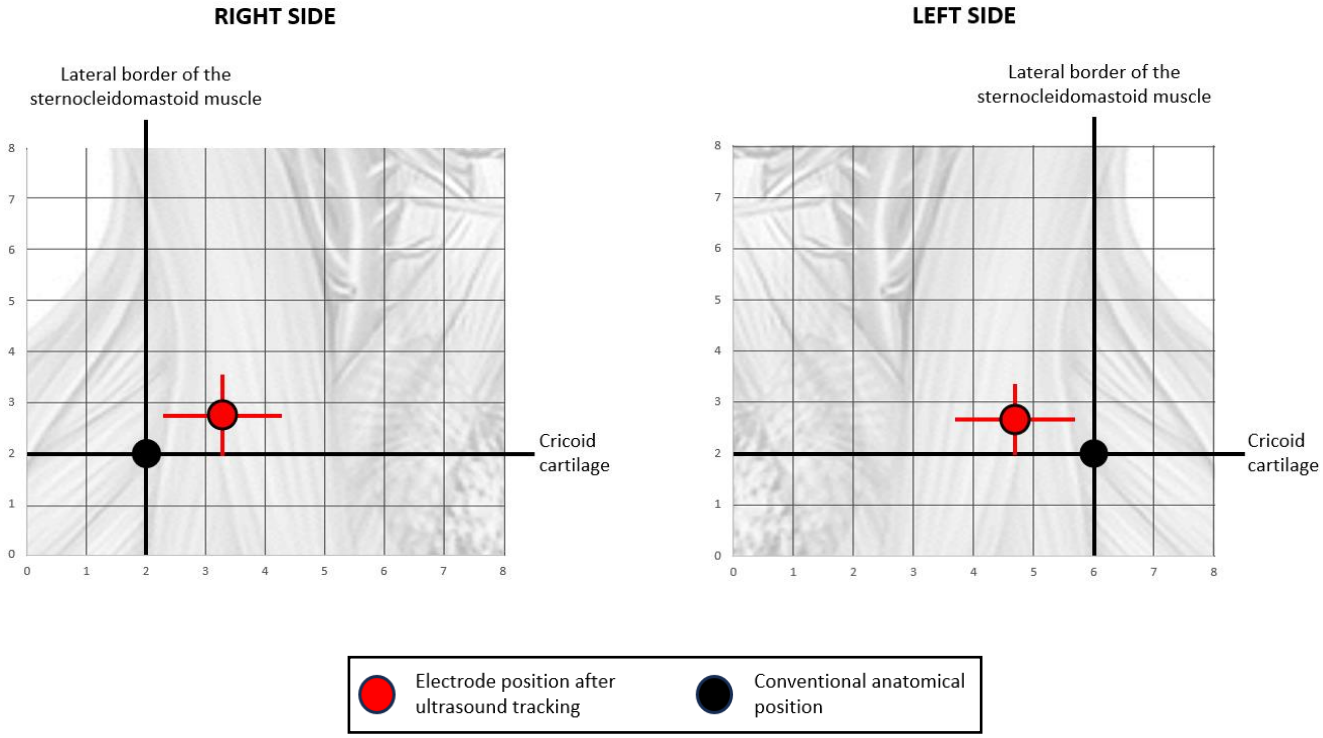
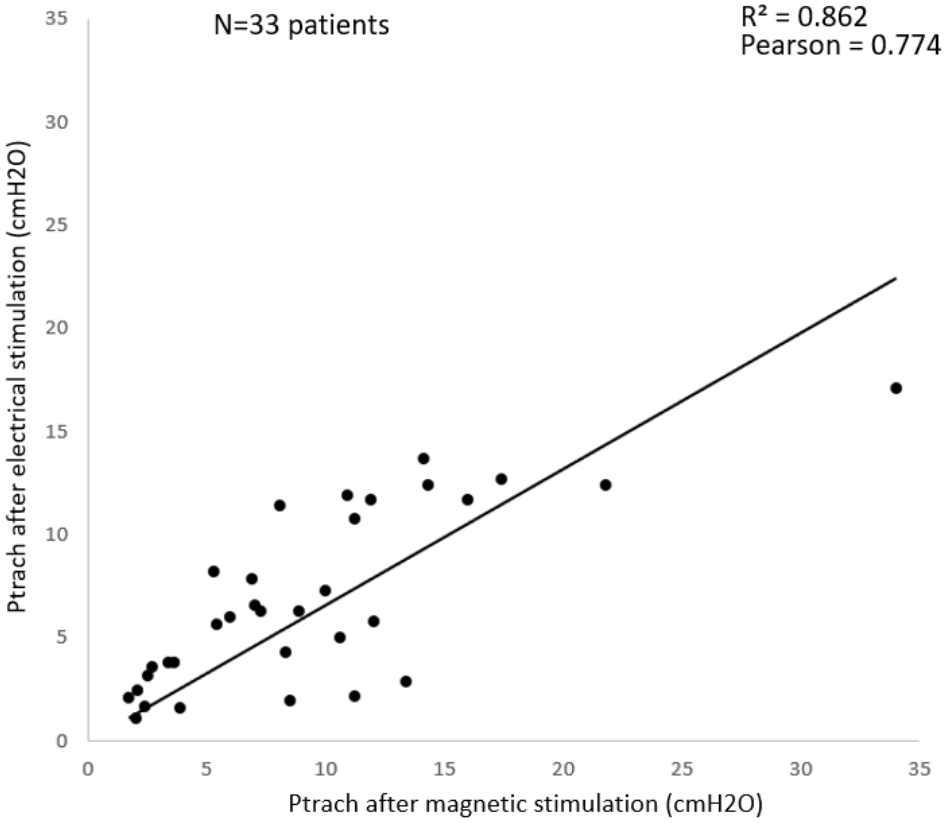


Figure S6: Correlation between electrical stimulation using Sonostim method and magnetic stimulation in patients with obesity.



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ORIGINAL ARTICLE

Shear Wave Elastography, a New Tool for Diaphragmatic Qualitative Assessment

A Translational Study

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Abstract

Rationale: Prolonged mechanical ventilation is often associated with either a decrease (known atrophy) or an increase (supposed injury) in diaphragmatic thickness. Shear wave elastography is a noninvasive technique that measures shear modulus, a surrogate of tissue stiffness and mechanical properties.

Objectives: To describe changes in shear modulus (SM) during the ICU stay and the relationship with alterations in muscle thickness. To perform a comprehensive ultrasound-based characterization of histological and force production changes occurring in the diaphragm.

Methods: Translational study using critically ill patients and mechanically ventilated piglets. Serial ultrasound examination of the diaphragm collecting thickness and SM was performed in both patients and piglets. Transdiaphragmatic pressure and diaphragmatic biopsies were collected in piglets.

Measurements and Main Results: We enrolled 102 patients, 88 of whom were invasively mechanically ventilated. At baseline, SM was 14.3 ± 4.3 kPa and diaphragm end-expiratory thickness was 2.0 ± 0.5 mm. Decrease or increase by more than 10% from baseline was reported in 86% of the patients for thickness and in 92% of the patients for SM. An increase in diaphragmatic thickness during the stay was associated with a decrease in SM ($\beta = -9.34 \pm 4.41$; $P = 0.03$) after multivariable analysis. In the piglet sample, a decrease in SM over 3 days of mechanical ventilation was associated with loss of force production, slow and fast fiber atrophy, and increased lipid droplets accumulation.

Conclusions: Increases in diaphragm thickness during critical illness is associated with decreased tissue stiffness as demonstrated by shear wave ultrasound elastography, consistent with the development of muscle injury and weakness.

Clinical trial registered with www.clinicaltrials.gov (NCT03550222).

Keywords: diaphragmatic dysfunction; diaphragmatic ultrasonography; mechanical ventilation; transdiaphragmatic pressure

(Received in original form November 6, 2020; accepted in final form July 12, 2021)

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Supported by departmental resources, an INSERM-transfer research grant, the Medical School of the Montpellier University Young Researcher Grant (Y.A.), and RegenFHU PhD Funding (A.F.).

Author Contributions: A.F. and Y.A. performed all the ultrasound measurements, analyzed the results, and participated in the manuscript editing. F.G. and D.C. contributed to the study design and patient enrollments. M.C. performed all transdiaphragmatic pressure measurements and contributed to the piglet model. F.R. performed all histological analyses. K.K. contributed to the study design. A.L., P.E., and S.M. reviewed some of the measurements and participated in the analysis results. S.J. contributed to the study design, analysis results, and manuscript editing. N.M. and L.G. performed statistical analysis. B.J. designed the study, participated in manuscript editing, and approved its final version.

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 204, Iss 7, pp 797–806, Oct 1, 2021
Copyright © 2021 by the American Thoracic Society
Originally Published in Press as DOI: 10.1164/rccm.202011-4086OC on July 13, 2021
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Diaphragm weakness is associated with poor outcomes in critically ill patients. Both decrease (atrophy) and increase (supposed injury) in diaphragmatic thickness are associated with prolonged ventilation. Shear wave ultrasound elastography provides additional information about muscle quality at rest by measuring shear modulus, a quantifiable measurement of tissue stiffness. Diaphragm mechanical properties, assessed by shear wave ultrasound elastography, have never been investigated in the critically ill population.

What This Study Adds to the Field: Our results show that the increase in diaphragmatic thickness in one-third of patients during their ICU stay is associated with a decrease in diaphragmatic shear modulus. Injurious changes in muscle, including muscle fiber atrophy and weakness, are associated with a decrease in shear modulus. These results suggest that shear modulus can detect an alteration in diaphragmatic mechanical properties and are in line with the diaphragmatic myotrauma concept.

Diaphragmatic weakness occurs in 30–60% of critically ill patients (1, 2). It can preexist ICU admission (3) or can appear during the ICU stay (4–6). Prolonged mechanical ventilation (MV) duration (6), increased incidence of weaning failure (3, 5, 6), prolonged ICU stay (3, 7), and long-term mortality (8) are associated with diaphragmatic weakness. MV and sepsis are the main risk factors (6, 9–11), and human biopsies have shown that diaphragmatic weakness is associated with muscle fiber lipid accumulation, inflammatory infiltrate, sarcomere injury, autophagy, and fiber atrophy (4, 12–14).

Ultrasonography is a user-friendly, noninvasive tool to explore the diaphragm at the bedside. Ultrasonography has been used to explore diaphragmatic contractile activity by measuring its excursion, thickening fraction, the velocity of diaphragmatic muscle motion (tissue Doppler imaging), and diaphragm mass using its thickness as a surrogate (15–19). In a landmark study, Goligher and colleagues reported that both diaphragmatic decrease of thickness and increase of thickness are associated with poor outcomes (20, 21). The authors then developed the "myotrauma" concept in which abnormal diaphragm function is associated with either overassistance (disuse atrophy) or underassistance myotrauma (muscle overuse leading to inflammation, edema, and injury) (22).

Shear wave ultrasound elastography (SWE) allows direct and real-time quantification of the mechanical properties of tissues and additional information about muscle quality at rest (23). Briefly, tissue deformation is created by an intrinsic focused push beam generated by the ultrasound probe. This results in the propagation of shear waves parallel to the surface of the probe. The velocity of these shear waves varies with mechanical properties of tissues (i.e., stiffness). Stiffness is then quantified by shear modulus (SM), which is calculated through shear wave propagation ($SM = \rho.v2$, in which ρ is the tissue density, equal to 1,000 kg/m^3 in the human body, and v is the shear wave velocity [m^2s^{-2}]) (24). By using inversion algorithms, this method maps the created wave velocity into elastograms and determines stiffness of the tissue by measuring the SM (25). A higher SM value corresponds to higher tissue stiffness. SWE provides a spatial representation and quantifiable measurement of the mechanical properties of the tissue (23). Although shear wave speed only depends on stiffness for large organs such as breast or liver, for thin structures such as the diaphragm, the shear wave travels approximately 50% faster when the structure's thickness doubles (26). Therefore, if the SWE decreases while thickness increases, it strongly suggests that the muscle's stiffness is decreased. Most of the available SWE studies have been published in the fields of limb muscles and tendons in chronic myopathy and in sports medicine (23, 27). Recently, two studies have evaluated SWE during diaphragmatic contraction and have suggested that SM can be a surrogate for diaphragm contractile activity in healthy volunteers (28, 29). Diaphragmatic SWE exploration is feasible in the critically ill population (30) with a previously reported reference value in this specific population at admission of 13.7 kPa (±4.4) (31), and healthy subjects' values at rest ranging from 6.2 kPa (±3.6) to 12 kPa (±2) (29, 30). Fossé and colleagues investigated changes in SM during diaphragm contraction in mechanically ventilated patients as a potential surrogate to transdiaphragmatic pressure (Pdi) (31). Changes in diaphragm SM at rest over time have never been investigated in the critically ill population. We hypothesized that change in SM, either higher or lower, may help to better describe the histological changes occurring in diaphragm muscle during critical illness (32). A drop in stiffness could reflect muscle fiber atrophy (33) or a combination of muscle edema, inflammatory or lipid accumulation, and fiber atrophy (34). An increase in SM could be due to exacerbated muscle fibrosis as in late-stage Duchenne's myopathy (35) or cerebral palsy (36).

The aim of this translational study was first to describe diaphragm thickness and SM changes during the ICU stay and then to explore the relationship between ultrasound measurements, diaphragmatic histology, and force production using diaphragm biopsies in a mechanically ventilated piglet model. Results were partially presented at the American Thoracic Society Annual Meeting (Dallas, Texas, May 17–22, 2019) (37).

Methods

Human Study Population and Setting

This prospective observational study was conducted in the medical ICU at the University Hospital of Montpellier, France, from December 2017 to June 2018 and included all consecutive patients with at least one organ failure (defined by the Sepsis-related Organ Failure Assessment score) (38) (*see* online supplement for details). Patients were included within 24 hours of admission regardless of the need for MV. Images in B mode for thickness and SWE mode for SM were obtained at baseline (Day 0), and repetitively every other day up to Day 28, discharge from the ICU, or death. Ultrasound diaphragm thickness may increase or decrease according to the combination of changes in all its components including the muscle fibers but also connective tissue, the vessels, inflammatory or lipid accumulation, and muscle edema. Institutional ethical approval was obtained (2017-CLER-MTP-09-16). We followed the STROBE guidelines for observational studies (39).

Shear Wave Elastography Imaging Procedure

In biomechanics, stiffness is defined by the proportional relationship between stress (the external force or compression) and strain (deformation) applied to it. Transmission of a longitudinal pulse leads to tissue displacement, which is detected by pulse echo ultrasound, and allows for the measurement of shear wave velocity (V in $m \cdot s^{-1}$) in the tissue. Shear wave velocity is proportional to SM (also named μ and expressed in kPa) using the formula: $\mu = \rho.v^2$ (in which ρ is the tissue density, equal to 1,000 kg/m^3 in the human body). Hard tissues have a higher SM and V than soft tissues (24).

An Aixplorer ultrasonic scanner (SuperSonic Imagine) was used with a 4- to 15-MHz linear transducer (SL15-4; SuperSonic Imagine) in both B and SWE modes with musculoskeletal preset. All images and measurements were performed by two operators (Y.A. and A.F.) according to a standardized and reproducible protocol (30) (*see* Methods, Figure E1, and Video E1 in the online supplement).

Patients were assessed in supine position, half sitting at 30°. Conscious subjects were instructed to remain relaxed and to breathe as calmly as possible throughout the procedure. We performed all measurements in triplicate on the right hemidiaphragm. Because contractile activity increases SM, we performed all the measurements at the end of expiration when the diaphragm is at rest. Conscious subjects were instructed to remain relaxed, to breathe as calmly as possible throughout the procedure, and to remain apneic at FRC for SWE acquisition as long as possible. For mechanically ventilated patients, an end-expiratory pause was applied during SWE acquisition. When a stable image with good quality criteria (homogeneous SWE color map) was not possible to collect, owing to high respiratory rate for example, the measured SM was not used for data analysis. Proofreading of the images was done offline and blinded by the two operators (A.F. and Y.A.). To enable replication of image location on repeated ultrasound assessments, a mark was carefully drawn on the subject's chest during the first measurement procedure and a standardized protocol was applied.

During image acquisition, transducers were placed with minimal compression on top of a generous amount of at least 5 mm of coupling gel to avoid distortion of the underlying tissue (40). The transducer was placed via an intercostal approach at the zone of apposition, in the sagittal plane perpendicular to the diaphragm muscle, and between the right anterior and midaxillary lines. The diaphragm was identified as a three-layered structure comprising two hyperechoic lines (pleural and peritoneal membranes) and a middle hypoechoic layer (diaphragm muscle fibers). Subsequently, the probe was oriented approximately 90° and finely adjusted to obtain a longitudinal view with the probe (and acoustic beam) parallel to the direction of the diaphragm muscle fascicles, and to obtain maximal echo intensity from diaphragm membranes. When activating the SWE mode, a color-coded box representing the region of interest was superimposed on the image. The widest area possible was drawn in the most homogeneous zone of the region of interest using built-in software of the ultrasound system (Q-Box trace) to avoid measurement bias, and SM was collected (Figure E1 and Video E1).

All acquired images and data were stored and secondarily analyzed as recommended by Nijholt and colleagues using Osirix DICOM Viewer software (Pixmeo) (41). The whole procedure, with image acquisition in B-mode frames and SM elastograms in triplicate, required 4–5 minutes at the patient's bedside

Mechanically Ventilated Piglet Studies

After approval by the University of Montpellier Institutional Ethics Committee for Animal Research and Care and according to the recommendations of the Helsinki Declaration, we conducted a piglet study to describe the association between diaphragm thickness and SM. Twelve piglets (25–35 kg) were sedated and mechanically ventilated in volume-controlled mode for 3 days as previously described (42). The detailed protocol is provided in the electronic supplement. Briefly, we used Pdi as the reference method for the assessment of diaphragm function (1). Pdi was calculated from esophageal and gastric pressure measurements. Pressure–frequency curves (Day 0–3) were measured daily by stimulating diaphragm contractions at end-expiration and using transvenous pacing catheters to achieve phrenic nerve stimulation with frequencies ranging from 20 to 100 Hz in a serial manner (43).

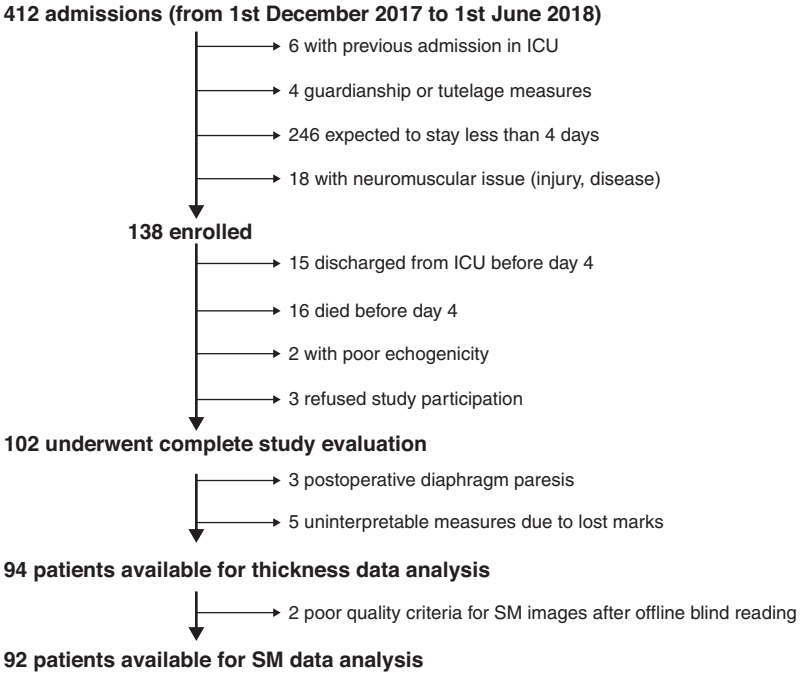


Figure 1. Study flow chart of critically ill patients. This figure shows the flow chart of patients admitted to our unit during the study. Consecutive patients with at least one organ failure and an expected duration of ICU stay ⩾3 days were enrolled. Of 412 adults, 138 were enrolled, 36 were excluded, and 102 completed the study evaluation. Ninety-four patients were available for analysis with at least three diaphragm evaluations. SM = shear modulus.

Diaphragm ultrasound-acquired images for thickness and SM measurement were recorded daily at the end of expiration when the diaphragm was at rest for all 12 piglets. Finally, diaphragm biopsies were obtained before euthanasia at Day 3 for 10 piglets (*see* Methods in the online supplement). Briefly, segments of dissected diaphragm strips were either immediately fixed for electronic microscopy examination and the quantification of intramuscular lipid droplets accumulation, or stained with hematoxylin/eosin for inflammatory cells infiltration and fiber types determination. Computer images captured from randomly selected microscopic fields were analyzed.

Endpoints

The two coprimary endpoints were to describe the evolution of diaphragm SM during the ICU stay and the association between diaphragm SM (as a surrogate for diaphragm stiffness) and thickness. Diaphragm thickness is a surrogate for the whole diaphragm muscle mass including the muscle fibers but also connective tissue, the vessels, inflammatory or lipid accumulation, and muscle edema.

The exploratory endpoints were to describe the association between diaphragm SM and the patients' clinical outcomes, and between diaphragm SM, fiber size, muscle inflammatory cells infiltration, muscular

Table 1. Demographics, Clinical Characteristics, and Outcomes of the Study Population

Characteristics	Study Population (*n* = 92)	Change in Diaphragm Shear Modulus during the First Week			*P* Value
		>10% Increase (*n* = 47)	<10% Change (*n* = 7)	>10% Decrease (*n* = 38)	
Age, yr	60 ± 17	62 ± 17	59 ± 16	55 ± 17	0.46
Sex, M	63 (70)	34 (72)	3 (43)	26 (72)	0.29
Body mass index, kg/m^2	26 ± 16	24 ± 5	24 ± 7	24 ± 6	0.64
SAPS II	58 ± 19	62 ± 20	50 ± 10	55 ± 18	0.11
SOFA score at admission	8 (5–11)	9 (5–11)	6 (5–6)	8 (6–11)	0.22
Comorbidities					
COPD	16 (17)	9 (19)	1 (14)	6 (16)	0.90
Ischemic heart disease	11 (12)	5 (11)	0 (0)	2 (5)	0.46
Chronic heart failure	17 (19)	5 (11)	0 (0)	12 (32)	0.02
Diabetes mellitus	20 (22)	7 (15)	1 (14)	12 (32)	0.16
Chronic kidney disease	13 (14)	9 (19)	1 (14)	3 (8)	0.33
Cancer	31 (34)	13 (28)	2 (29)	16 (42)	0.36
Cirrhosis	5 (5)	1 (2)	2 (29)	2 (5)	0.02
Inflammatory disease	7 (8)	5 (11)	0 (0)	2 (5)	0.47
Chronic corticosteroid treatment	21 (23)	13 (28)	1 (14)	7 (18)	0.20
Malnutrition	22 (24)	9 (19)	2 (29)	11 (29)	0.35
Sepsis-3 criteria within first week	72 (78)	35 (74)	6 (86)	31 (82)	0.87
Primary reason for admission					
Respiratory distress	52 (56)	27 (57)	4 (57)	21 (55)	0.98
Cardiac arrest	9 (10)	4 (8)	1 (14)	4 (11)	0.87
Acute heart failure	3 (3)	2 (4)	0	1 (3)	0.41
Coma – Encephalopathy	10 (11)	5 (11)	2 (29)	3 (8)	0.27
Sepsis	12 (13)	5 (11)	0	7 (18)	0.32
Other	6 (7)	4 (9)	0	2 (5)	0.64
Clinical management during ICU stay					
Use of NMBA	55 (60)	28 (60)	6 (86)	21 (55)	0.32
Duration of NMBA infusion, d*	3 (2–5.5)	3 (2–4.5)	8 (6–18)	3 (2–6)	0.30
Use of corticosteroids	51 (55)	32 (68)	3 (43)	16 (42)	0.35
Duration of corticosteroid infusion, d*	8 (4–12.3)	8 (3.8–11)	8 (4–12.5)	5 (4.3–8)	0.62
Use of aminoglycosides	29 (32)	14 (30)	0 (0)	15 (39)	0.11
Use of sedatives	79 (86)	40 (85)	6 (86)	33 (87)	0.50
Duration of deep sedation, d*	5 (3–9)	5.5 (2.3–8)	8 (4–8.5)	4 (3–9)	0.41
Duration of invasive MV, d*	7 (4–15)	7.2 (2.8–13.5)	8 (7.4–18)	7 (4–15.2)	0.41
Duration of CMV, d*	2.8 (1.1–5.7)	2.7 (0.9–5.4)	4.4 (3.3–6)	2.8 (1.6–5.6)	0.41
No need for ventilation	13 (14)	7 (15)	1 (14)	5 (13)	0.38
Need for vasopressors	78 (85)	41 (87)	4 (57)	33 (87)	0.11
Duration of vasopressor infusion, d*	4 (3–7)	4 (3–6)	4 (2.8–7.8)	4 (3–7)	0.41
Need for dialysis	24 (26)	14 (30)	1 (14)	9 (24)	0.62
Duration of dialysis, d*	6 (3–8.5)	7 (4–12.5)	1 (1–1)	4 (3–7)	0.28
Cumulative fluid balance at Day 3, L	4.7 ± 4.4	4.4 ± 4.7	3.7 ± 2.6	5.2 ± 4.3	0.83
Cumulative fluid balance at Day 7, L	5.5 ± 5.4	5.1 ± 5.7	4.4 ± 4.9	6.1 ± 5.3	0.81

Definition of abbreviations: CMV = controlled mechanical ventilation; COPD = chronic obstructive pulmonary disease; MV = mechanical ventilation; NMBA = neuromuscular blockade; SAPS II = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.
Data are presented as *n* (%), mean ± SD, or median (interquartile range). Two out of 94 patients could not have shear modulus measurements and were therefore removed from this table.
*Results are presented for patients who received the mentioned therapy.

lipid droplets accumulation, and force production (measured by Pdi) in mechanically ventilated piglets.

Statistical Analysis

The study population was divided into three groups (increase, decrease, or stable) based on the overall change in diaphragm thickness (thickness groups) or SM (SWE groups), from the baseline measurement to the last measurement obtained during the first week in the ICU using a 10% cutoff value (20). This cutoff was chosen because it was clinically relevant according to previous studies about SWE in limb muscles (23, 35) and was in agreement with the measurement of variance identified in our previous study (30).

Descriptive statistics are reported as numbers (%), means ± SD, or medians (interquartile range) and compared as appropriate. A mixed linear regression was used for the analysis. Repeated measures correlation coefficient (R) was used for determining overall relationships between variables. Covariates were tested in the model (if $P < 0.15$ in the univariate analysis), selected in a backward selection procedure, and then presented as a regression coefficient with 95% confidence intervals. A nonlinear effect for continuous variables was tested using a polynomial model. Akaike information and Bayesian information criteria were used to assess the nonlinearity. For all final comparisons, a P value $\leqslant 0.05$ was considered statistically significant. Statistical analysis was conducted using SAS version 9.3 (SAS Institute).

Results

Demographics and Ultrasound Measurements at Baseline

Between December 2017 and June 2018, 102 critically ill patients were enrolled and at least three ultrasound evaluations of thickness and SM were respectively available for 94 and 92 of them (Figure 1). Demographic data and clinical characteristics are reported in Table 1. At Day 0, 67 patients (71%) were mechanically ventilated. The duration of MV was 7 (4–15) days, 2.8 (1.1–5.7) days being spent in controlled mode. We collected 637 and 631 ultrasound measurements for thickness and SM, respectively, after excluding 42 and 38 images for poor quality criteria. On ICU admission, diaphragm end-expiratory thickness was 2.0 ± 0.5 mm and SM was 14.3 ± 4.3 kPa. In the 12 mechanically ventilated piglets, baseline end-expiratory thickness and SM were 2.3 (2.1–2.5) mm and 16.4 ± 4.3 kPa, respectively.

Change in Diaphragm Thickness and Diaphragm SM Over Time

In critically ill patients overall, diaphragm thickness did not significantly change during the first week of the ICU stay (2.0 ± 0.5 mm on admission vs. 1.8 ± 0.4 mm at Day 7; $P = 0.24$). Diaphragm thickness change showed heterogeneous patterns in the critically ill patients. It remained unchanged in 13 patients (14%), decreased by more than 10% in 46 patients (49%), and increased by more than 10% in 35 patients (37%) (Figure E2). In critically ill patients, diaphragm SM remained unchanged in 7 patients (8%), decreased by more than 10% in 38 patients (41%), and increased by more than 10% in 47 (51%) patients (Figures 2 and E3). In multivariable analysis, diaphragm SM dropped over time in older patients ($P < 0.05$), in patients treated for sepsis ($P = 0.03$) or with steroids ($P = 0.01$), and in patients showing increased diaphragmatic thickness during the ICU stay ($P = 0.03$) (Table 2). Time spent under controlled MV was associated with a decrease in SM in comparison with time spent under pressure support ventilation or without ventilatory assistance ($P < 0.05$) (Table 2).

In piglets, diaphragm SM decreased between Day 0 and Day 3 (16.4 ± 4.3 kPa vs. 14.1 ± 3.1 kPa [$P = 0.07$]), when diaphragm thickness did not (2.3 ± 0.4 mm vs. 2.3 ± 0.4 mm, $P = 0.18$) (Figure 3A). When using the same 10% cutoff change in SM as in critically ill patients, SM remained unchanged in six piglets and decreased by more than 10% in six piglets. No correlation was found between absolute diaphragm thickness and SM values (Figure 3B).

SM, Muscle Fiber Size, Inflammatory Cells Infiltration, Lipid Accumulation, and Pdi

To better understand the drop in SM over time, we evaluated the relation between SM and diaphragm ultrastructure in mechanically ventilated healthy piglets for 3 days. A decrease in SM during the 3-day experiment was associated with a smaller fast- and slow-twitch fiber cross-sectional

Table 2. Factors Associated with Changes in Diaphragm Shear Modulus and Thickness during ICU Stay: Adjusted Multivariable Analysis

		Diaphragm Shear Modulus as a Quantitative Value		
Risk Factors	**(/ Reference)**	**β**	**SD**	***P* Value**
Sepsis	Yes / No	−1.79	0.82	0.03
Ventilation mode				<0.01
	Assisted / Controlled	1.45	0.40	
	No MV / Controlled	2.85	0.47	
Age		−0.05	0.02	<0.05
Days under deep sedation		0.14	0.07	0.05
Days on corticosteroids		−0.11	0.04	0.01
Diaphragm thickness		−8.92	4.46	0.03
		Diaphragm Thickness as a Quantitative Value		
Sex	M / F	0.03	<0.01	<0.01
Diaphragm shear modulus		<−0.01	<0.01	<0.01
Days of invasive MV		<−0.01	<0.01	<0.01

Definition of abbreviation: MV = mechanical ventilation.
Adjusted on day of measurement, and global number of days under MV. Deep sedation was defined as a Richmond agitation sedation scale of −3 to −5. Variables included in the model are those with $P < 0.15$. *See* Table E1 for thickness and Table E2 for shear modulus. Shear modulus model variables: sepsis, difficult weaning, ventilation mode, age, ventilation-free days, days under vasopressors, days under deep sedation, days on corticosteroids, and diaphragm thickness. Thickness model variables: sex, ventilation mode, diaphragm shear modulus, days under deep sedation, days of invasive MV, and septic shock.

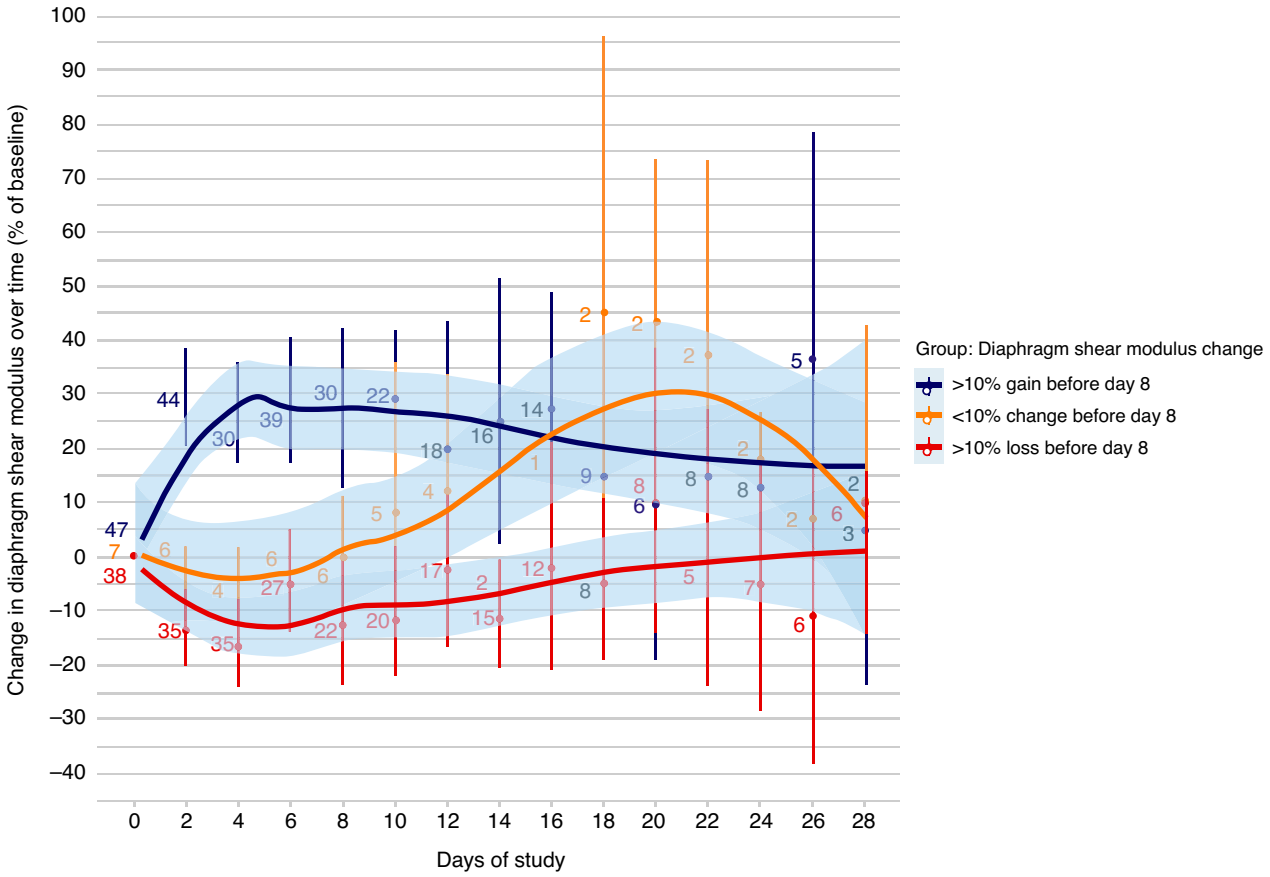


Figure 2. Variation in diaphragm shear modulus over time obtained in critically ill patients. Percentage of change from baseline (enrollment day) is represented on the *y*-axis and days of follow-up on the *x*-axis. Subjects are categorized into three groups according to the magnitude and direction of change in diaphragm shear modulus during the first week of the ICU stay using a 10% cutoff value. Mean and SD are plotted for each group on each study day. Numbers shown next to each data point indicate the number of measurements on each study day. Shared area indicates confidence intervals. Trend line and confidence intervals (shaded area) were fitted by Loess smoothing.

area demonstrating diaphragm fiber atrophy (Figures 3C and 3D) and with higher lipid vacuoles accumulation (Figures 3F and 3G). No difference was found with respect to inflammatory cells infiltration (Figures 3H and 3I).

Furthermore, the decrease in SM was associated with diaphragm loss of force measured by Pdi (Figures 3E and E5).

Patient Outcome

Ventilator-free days, ICU length of stay, weaning difficulty, and mortality at Day 28 were not significantly associated with change in diaphragm SM or thickness (Tables 3 and E5).

Discussion

The study demonstrates a heterogeneous pattern of changes in SM during the first week of ICU stay, in which SM does not change in 8%, increases in 51%, and decreases in 41% of patients. Changes in SM were negatively related to changes in diaphragm thickness in critically ill patients after multivariate analysis. Decrease in SM was associated with diaphragm fiber atrophy, diaphragm lipid accumulation, and loss of force production in a healthy mechanically ventilated piglet model. The apparent increase in diaphragm thickness during the ICU stay may therefore be linked with an alteration of diaphragmatic ultrastructural and mechanical properties, as suggested in the diaphragm myotrauma concept.

SWE provides a reliable quantifiable measurement of muscle mechanical properties and muscle stiffness (40, 44) and therefore has been suggested as a tool to evaluate muscle quality and changes of *in vivo* mechanical properties over time (23, 40). SWE is routinely used to evaluate tendon injuries in sports medicine and muscle mechanical properties in muscular diseases (45, 46). According to muscle stiffness change occurring during diseases, SM would be either increased or decreased. For instance, increased SM has been observed in late-stage Duchenne's myopathy, which is associated with muscle fibrosis (35), or in the affected and stiff limb consecutive to cerebral palsy (36). Conversely, conditions associated with inflammation, edema, and muscle swelling (e.g., ultramarathons, myositis) have been associated with loss of stiffness and decreased SM (34, 46). Decreased SM has also been associated with denervated muscle atrophy (33). Although recent studies reported that SM of the diaphragm was correlated with diaphragm force production during inspiratory efforts (28, 29, 31), no study has evaluated SWE of the diaphragm in the

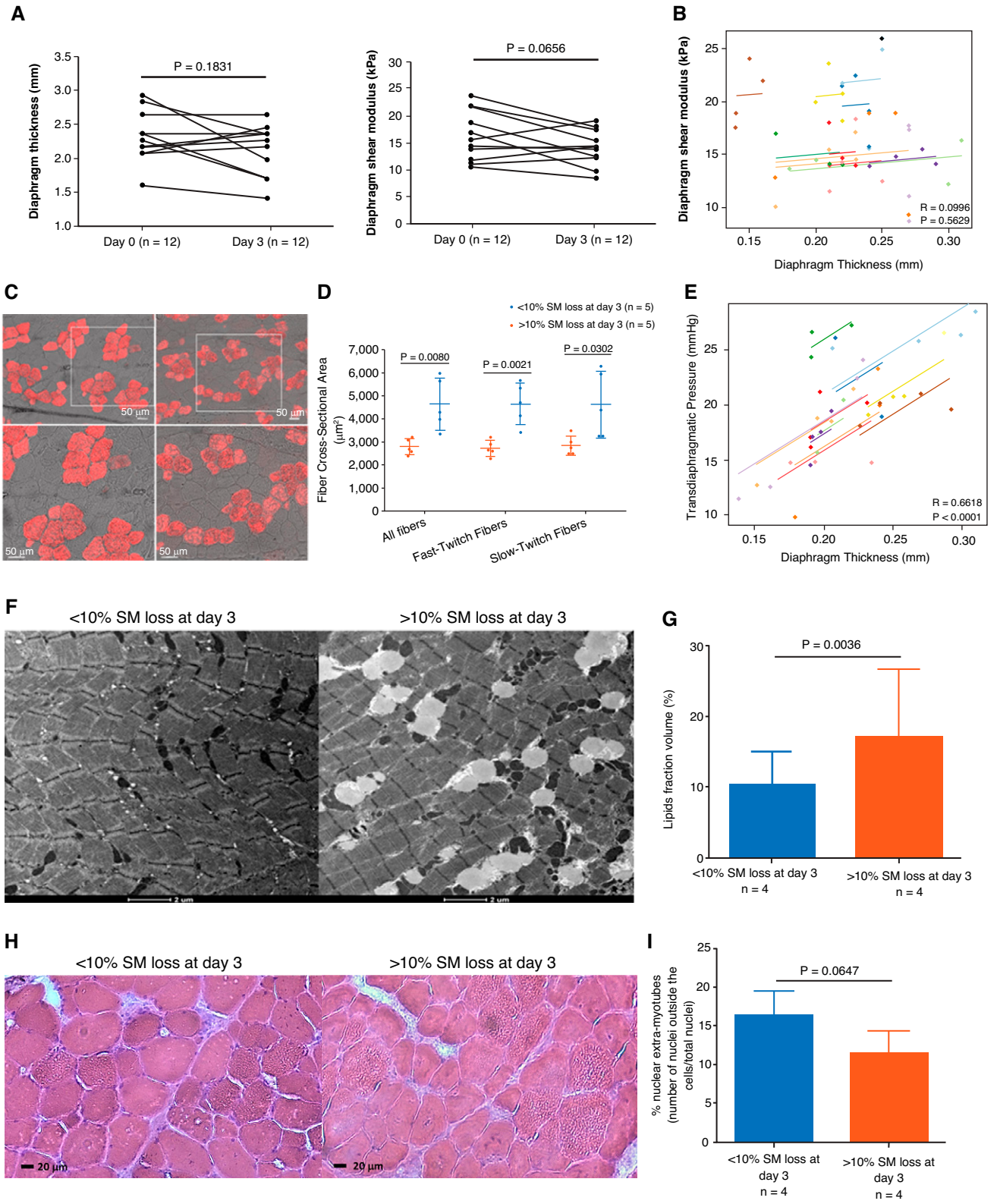


Figure 3. (*A–I*) Relationship between diaphragm shear modulus, (*A* and *B*), diaphragm thickness, (*C* and *D*) diaphragm muscle fiber size, (*E*) diaphragm force production, (*F* and *G*) diaphragm lipid accumulation, and (*H* and *I*) diaphragm inflammatory infiltration obtained in mechanically ventilated healthy piglets. (*A*) Quantitative analyses of the diaphragm thickness (left panel) and the diaphragm shear modulus (SM) (right panel) at Day 0 (circles) and after 3 days of mechanical ventilation (MV) (squares). (*B*) Relationship between thickness and SM for all

Table 3. Univariate Analysis of Outcomes According to Change in Diaphragm Shear Modulus over Time

Outcomes	Study Population (*n* = 92)	Change in Diaphragm Shear Modulus during the First Week			*P* Value
		>10% Increase (*n* = 47)	<10% Change (*n* = 7)	>10% Decrease (*n* = 38)	
Ventilator-free days to Day 28*	18.4 (3.8–24.1)	19.2 (4.1–25.1)	5.3 (0–20)	15 (3.8–24)	0.21
Ventilator-free days to Day 28† (*n* = 79)	15.5 (3.6–22.2)	16.9 (3.7–22.6)	5.2 (0.1–19.8)	13.7 (3.5–22.7)	0.48
Prolonged or difficult weaning† (*n* = 70)	35 (50)	16 (44)	4 (80)	15 (52)	0.30
Tracheostomy*	4 (4.4)	1 (2)	1 (14)	2 (5)	0.31
ICU mortality*	21 (23)	9 (19)	2 (29)	9 (24)	0.74
Day-28 mortality*	19 (20)	9 (19)	2 (29)	8 (22)	0.83
ICU length of stay, d*	12.4 (7.1–19)	12.2 (7.5–18.6)	12 (8.5–39)	13.1 (6.3–19.6)	0.82

Data are presented as *n* (%) or median (interquartile range).
*Results are presented for the total study population (92 patients).
†Results are presented for patients who received the mentioned therapy.

critically ill population as a surrogate for muscle quality or to follow up its architectural changes over time.

In the present study, diaphragm SM as well as thickness changes over time did present different patterns (Figures 2 and E2). After adjustment for day of measurement and number of days on MV, thickness and SM changes over time appeared inversely associated (Table 2). Assuming the theoretical increase in shear wave speed when thickness increases (26), a positive correlation was expected if mechanical properties and stiffness of the analyzed tissue remained similar. Thus, the present negative correlation between diaphragm thickness and SM changes over time is even more valuable. These results indeed demonstrate that the diaphragm's stiffness is reduced because the shear wave speeds decrease with increasing thickness. After multivariable analysis, aging, sepsis, steroids, duration of MV, and the absence of spontaneous breathing cycles were associated with a decrease in diaphragm SM (Table 2). Conversely, one-fourth of the patients did show an increased SM and decreased thickness, which may represent a combination of decreased muscle mass, myofibrillar destruction, fiber atrophy, and muscle fibrosis (Table E9 and Figure E7).

Aging is associated with sarcopenia, myosteatosis, and myofibrosis. In a clinical study involving different age groups of volunteers, aging was associated with a decline in skeletal SM correlated with muscle weakness, which is in line with the present study (47). The decrease of SM in patients with sepsis in our study may be the consequence of the combination of atrophy, inflammation, edema, and lipid accumulation that reduce diaphragm stiffness (48). The effects of short-term corticosteroids on the diaphragm in critically ill patients is complex because corticosteroids both downregulate protein synthesis and promote atrophy but may also limit disease-related myositis thus with an unpredictable effect on muscle stiffness (11). A recent study showed that SWE detected decreased muscle stiffness associated with weaker muscles over time in patients on long-term glucocorticoid (49). Interestingly, we observed that changes in diaphragm thickness and in SM occurred in 80% of the 14 nonventilated patients, confirming that both MV and critical illness target the respiratory muscles before (3) or during the ICU stay (50).

To better understand the link between diaphragm histology and SM, we performed a 3-day MV piglet study and biopsied the diaphragm at the end of the experiment. We report herein for the first time that the decrease in SM was associated with both slow and fast fiber atrophy (Figures 3C and 3D), higher intramuscular lipid vacuoles content (Figures 3F and 3G), and diaphragm loss of force production (Figures 3E and E4).

The lack of difference in inflammatory cells infiltration between SM groups in piglets may be related with the healthy state of this model, with less systemic inflammation like sepsis or circulatory shock (51). These findings are in line with the compelling diaphragm myotrauma concept in which underassistance may lead to muscle injury, edema, and inflammation (22). The model of healthy mechanically ventilated piglet is a model of diaphragm overassistance that may explain the increased diaphragm lipid content. Picard and colleagues showed that resting diaphragm during controlled MV may indeed be associated with a state of relative energetic oversupply versus demand that would trigger mitochondrial dysfunction

Figure 3. (*Continued*). values during 72 hours of MV. (*C*) Representative images of transverse frozen sections stained with antibodies directed against slow isoforms of myosin heavy chain (red), according to SM decrease at Day 3: specimens with a decrease in the SM of <10% (left panels) and a decrease in the SM of >10% (right panels). Scale bars, 50 μm. (*D*) Quantitative analyses of diaphragm fiber cross-sectional area (median and quartiles) according to SM decrease at Day 3. (*E*) Relationship between transdiaphragmatic pressure after supramaximal phrenic nerve stimulation at a frequency of 100 Hz and diaphragm SM for all values during 72 hours of MV. (*F*) Representative electron micrographs showing diaphragm lipid droplets accumulation according to SM decrease at Day 3: SM decrease <10% (left panel) and SM decrease >10% (right panel). Scale bars, 2 μm. (*G*) Quantitative analyses of diaphragm lipid droplets accumulation (mean ± SD) according to SM decrease at Day 3. (*H*) Representative images of hematoxylin and eosin–stained sections for inflammatory cells infiltrate according to SM decrease at Day 3: SM decrease <10% (left panel) and SM decrease >10% (right panel); extracellular nuclei of an inflammatory cell are colored in purple. (*I*) Quantitative analyses of diaphragm inflammatory cells infiltrate (mean ± SD) according to SM decrease at Day 3. All extracellular nuclei outside the muscle fibers were assumed as inflammatory cells, and their presence was expressed as a percentage of the extracellular nuclei out of total nuclei in the area.

and oxidative stress (13). Diaphragm inflammation and edema may be the main hypothesis for decreased SM in critically ill patients with overuse injury (34, 52). We summarized the different hypothesis for diaphragm SM and thickness changes in Table E9.

The perspective of the present results and the recent literature (29, 31) is that diaphragm SM evaluation in critically ill mechanically ventilated patients may be used as a tool in future interventional studies that would aim to promote diaphragm protective strategies. It may also help in phenotyping patients according to their diaphragm profile using both diaphragm mass surrogate (thickness) and diaphragm mechanical properties (SM). Finally, SM has been described as a surrogate of inspiratory muscles effort in spontaneously breathing patients.

Our study presents limits that should be discussed. First, we did not perform serial biopsies of the diaphragm in patients, a dangerous procedure outside the operating room. We therefore could only describe the association between ultrasound measurements and biopsy findings in the piglet model. Diaphragm fiber atrophy was associated with a decreased SM in piglets. Second, to ensure the highest reproducibility, we performed the ultrasound measurements at the end of expiration (and carefully checked the absence of diaphragm contraction) (20). However, because this study was designed as a "real life" study, we did not use Pdi monitoring to make sure none of the measurements were performed above the FRC. Third, we performed more than 600 ultrasound examinations from ICU admission to discharge, increasing the statistical power of the analysis, but we analyzed a combination of different ventilatory conditions (Figure E5). To date, longitudinal studies have been heterogeneous, with follow-up being cut off right after extubation (53) at Day 5 (50) or at Day 14 (20). Our study design is a limit but also better reflects the journey of the ICU stay. Finally, although the present combination of both critically ill patients mechanically ventilated for 7 days and healthy piglet model ventilated for 3 days illustrate the myotrauma concept, it may be difficult to extrapolate some data from one model to the other.

In summary, we show for the first time that both diaphragm thickness and stiffness change vary heterogeneously during the ICU stay. The increase in global diaphragm thickness during the ICU stay in one-third of the patients is associated with a drop in diaphragm stiffness. In a mechanically ventilated piglet model, we report that the decrease in diaphragm stiffness from Day 1 to Day 3 is associated with fast and slow fiber atrophy, diaphragm lipid accumulation, and loss of diaphragm force production. Our results could be another building block to corroborate the myotrauma concept in which increase in diaphragm thickness marks a different yet not independent type of diaphragm injury than the better-known decreased thickness. Further studies focusing on better understanding cellular and molecular changes associated with changes in diaphragm thickness and stiffness over time are warranted to investigate whether increased thickness associated with decreased stiffness is a noninvasive indicator of diaphragmatic inflammation, lipid accumulation, injury, and edema, associated with the fiber atrophy previously described in piglets. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Claudine Gniadek (R.N.) and the members of the medical and nursing team for their participation in the present study. They also thank the animal laboratory facility at the medical school (Plateau Technique de Recherche Experimentale, Nîmes, France) for their technical support and Mrs. Rama Levin for her help in English editing for the manuscript. They thank Christophe Cassinoto (M.D., Radiology Unit, Montpellier Teaching Hospital) for his help with the short video presented in the online supplement.

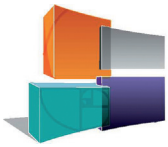
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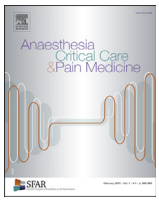
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Anaesth Crit Care Pain Med 38 (2019) 429–430





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Editorial

What is the most appropriate spontaneous breathing trial before extubation in ICU ventilated patients?



ARTICLE INFO

Keywords:
ICU
Invasive mechanical ventilation
Weaning

Mechanical ventilation, which is the most used organ replacement therapy in intensive care unit (ICU), is a life-saving intervention. In the ICU, the timing of liberation from invasive mechanical ventilation is an important issue for clinicians treating critically ill intubated patients receiving invasive mechanical ventilation [1–3]. After resolution of acute illness, or in other words when the resolution or improvement of the condition leading to intubation are done, mechanically ventilated patients are liberated from the ventilator, a process termed "weaning" from mechanical ventilation [4–6]. Weaning and extubation, though following each other in clinical practice, are two separate processes that pose distinct problems. Separating the ventilator from the patient (weaning) and removing the tracheal tube (extubation) are challenging issues [1]. Indeed, if the patient remains intubated too long, complications associated with prolonged invasive mechanical ventilation may appear [7]. On the other hand, if the patient is extubated too early, reintubation, which could occur in 5 to 25% of cases, is associated with higher morbidity and mortality [1–8].

Before extubation, it is recommended to perform a "weaning test", which consists of a "spontaneous breathing trial" (SBT) [5,9]. The SBT aims to evaluate how the critically ill patient is able to breath "alone" with no ventilatory assistance. In the standard of care, two main weaning tests are suggested for non-selected adult patients: a T-piece trial (oxygen supply without positive pressure) and low pressure support ventilation (PSV), with a low level of PSV without positive end expiratory pressure (PEEP), from 5 to 7 cmH_2O, to compensate for the imposed workload due to the endotracheal tube and ventilator circuit [5]. In case of presence of a heated and moisture exchanger, the low level of PSV set should take into account the imposed workload due to the additional dead space, which is evaluated from additional 2 to 5 cmH2O PSV level.

Although these two weaning tests are not equivalent in terms of work of breathing (WOB) [10], no study has yet assessed the risk of extubation failure. Therefore, both weaning trials are recommended to assess whether a patient is ready to be extubated [5,11]. Moreover, the duration of the weaning test is also a subject of controversy ranging from a "short" 30-minute to a "long" 120-minute period.

In a recent Spanish clinical trial, Subira et al. [12] compared two different SBT techniques in 1153 mechanically ventilated patients in 18 ICUs. One was a "long" 120 minutes T-piece SBT ("highly demanding") and the other was a "short" 30 minutes low-PSV SBT ("less demanding"). In both groups, patients who successfully completed their SBT were extubated. The authors reported that patients in the 30 minutes low-PSV SBT group were more likely to be extubated compared to patients in the 120 minutes T-piece SBT group. Successful extubation occurred in 82% of patients in the low-PSV group and in 74% of patients in the T-piece group ($P = 0.001$). Worthy of note is that patients in the PSV SBT group did not experience a significant higher reintubation rate in the 72 hours after extubation (11% vs. 12%, $P = 0.63$). No significant difference was shown for ICU length of stay (median 9 days *vs.* 10 days; $P = 0.69$) or hospital length of stay (median 24 days *vs.* 24 days ($P = 0.45$). In comparison with patients in the T-piece group, those in the low-PSV group had significantly lower hospital mortality (10% *vs.* 15% [$P = 0.02$]) and 90-day mortality (13% *vs.* 17% [$P = 0.04$]).

The authors [12] should be congratulated for performing the largest randomised clinical trial ever conducted comparing the two common SBT techniques (T-piece *vs.* low PSV). They add a new piece to the puzzle of the weaning process in the overall non-selected patients. Their findings suggest that most patients can be tested for a short 30-minute period using a so-called "low-PSV" level of 8-cmH2O and zero PEEP. Moreover, using the low-PSV SBT add a safety process as the patient is continuously monitored for the main physiological respiratory variables (respiratory rate, tidal volume, minute ventilation…).

Future research should evaluate which additional prophylactic strategies could be associated to the optimal SBT, with the aim to

https://doi.org/10.1016/j.accpm.2019.09.005
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increase the success rate of extubation [13]. It could be proposed to evaluate:

- the optimal analgesia-sedation protocol as the weaning process of both analgesia-sedation and ventilator weaning are always linked [7];
- the use of reconnection to ventilator before extubation that was associated with reduced reintubation rate at 48 hours in a recent study [14] (reconnection to ventilator was made in 25% of included patients in the Subira study [12]);
- prophylactic non-invasive ventilation after extubation [15,16] (prophylactic non-invasive ventilation was performed in 9% of the low-PSV group and in 6% of the T-piece group in the Subira study [12]);
- the use of prophylactic high-flow nasal oxygen cannula after extubation [17–19] (which was made in 16% of the low-PSV group and in 13% of the T-piece group in the Subira study [12]).

In summary, the Subira study [12] suggests that for the majority of "easy to wean patients", a short 30-minute period using a so-called "low-PSV" level of 8-cmH2O and zero PEEP could be proposed as first line approach before extubation as SBT test.

Disclosure of interest

Pr. Jaber reports receiving consulting fees from Drager, Fisher & Paykel and Fresenius. The other authors declare that they have no competing interest.

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BMJ Open

Which spontaneous breathing trial to predict effort to breathe after extubation according to five critical illnesses: the cross-over GLOBAL WEAN study protocol

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To cite: Capdevila M, De Jong A, Aarab Y, *et al*. Which spontaneous breathing trial to predict effort to breathe after extubation according to five critical illnesses: the cross-over GLOBAL WEAN study protocol. *BMJ Open* 2023;**13**:e070931. doi:10.1136/bmjopen-2022-070931

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-070931).

Received 09 December 2022
Accepted 28 June 2023

Check for updates

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ABSTRACT

Introduction Readiness to be freed from ventilatory support can be evaluated by spontaneous breathing trial (SBT) assessing the patient's ability to sustain respiratory effort after extubation. Current SBT practices are heterogenous and there are few physiological studies on the topic. The objective of this study is to assess which SBT best reproduces inspiratory effort to breathe after extubation depending on the patient's illness.

Methods and analysis This will be a multicentre randomised cross-over physiological study, in a large population, in the era of modern intensive care units using last generation modern ventilators. Each included patient will perform three 15-minute SBTs in a random order: pressure support ventilation (PSV) level of 7 cmH_2O with positive end expiratory pressure (PEEP) level of 0 cmH_2O, PSV 0 cmH_2O with PEEP 0 cmH_2O and T-piece trial. A rest period of baseline state ventilation will be observed between the SBTs (10 min) and before extubation (30 min). Primary outcome will be the inspiratory muscle effort, reflected by pressure time product per minute (PTPmin). This will be calculated from oesophageal pressure measurements at baseline state, before and after each SBT and 20 min after extubation. Secondary outcomes will be PTPmin at 24 hours and 48 hours after extubation, changes in physiological variables and respiratory parameters at each step, postextubation respiratory management and the rate of successful extubation. One hundred patients with at least 24 hours of invasive mechanical ventilation will be analysed, divided into five categories of critical illness: abdominal surgery, brain injury, chest trauma, chronic obstructive pulmonary disease and miscellaneous (pneumonia, sepsis, heart disease).

Ethics and dissemination The study project was approved by the appropriate ethics committee (2019-A01063-54, Comité de Protection des Personnes TOURS - Région Centre - Ouest 1, France). Informed consent is required, for all patients or surrogate in case of inability to give consent.

Trial registration number NCT04222569.

STRENGTHS AND LIMITATIONS OF THE STUDY

⇒ Robust methodology with a randomised cross-over design.
⇒ Three spontaneous breathing trials evaluated.
⇒ The largest population for a physiological study on the topic.
⇒ Subgroup analysis on specific critical illnesses.
⇒ The main limitation is the short 48-hour follow-up.

ADMINISTRATIVE INFORMATION

This manuscript is written in accordance with SPIRIT guidelines.[1] The administrative information is described in table 1.

INTRODUCTION

Background and rationale

Mechanical ventilation is a life-saving intervention and the main organ support in intensive care units (ICUs). After recovery from acute illness, the patient is separated from the ventilator (weaning) and the endotracheal tube is removed (extubation). Predicting whether a critically ill patient can be successfully extubated is challenging. Readiness to be freed from ventilatory support can be evaluated by a spontaneous breathing trial (SBT)[2] assessing the patient's ability to sustain respiratory effort after extubation.[3]

Many SBT methods have been described and are used in ICUs around the world.[3–7] The most common SBTs are low pressure support ventilation (PSV) with or without positive end expiratory pressure (PEEP) (55%–72%) and T-piece trial (9%–59%).[4 6] The persistent diversity of practice reflects how controversial this topic is. A physiological meta-analysis from Sklar *et al* published in 2017,[3] including 16 studies and

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Table 1	
Title	Which spontaneous breathing trial predict effort to breathe after extubation according to five critical illnesses (or phenotypes): the cross over GLOBAL WEAN study protocol.
Trial registration	Trial identification number NCT04222569 (registered January 10th, 2020). All items can be found in the protocol.
Protocol version	April 11, 2023, version 5
Contact information for the trial sponsor	Principal investigator: Prof Samir JABER University of Montpellier Saint-Eloi Hospital, Intensive Care Unit & Anesthesiology Department B, Montpellier, France; 80 avenue Augustin Fliche. 34 295 Montpellier Cedex 5, France Tel: 00. 33. 467. 337. 271; Fax: 00. 33. 467.337. 448 E-mail: s-jaber@chu-montpellier.fr
Role of study sponsor	The sponsor has a funding and support role. This is a researcher-driven study, the principal investigator is actively involved in the study design, data collection, management, analysis and interpretation, writing of the report, and decision to submit the report for publication.
Role of coordinating centre	The Clinical Research and Innovation Department of the Montpellier University Hospital is involved in the coordination, monitoring, and good practices of the clinical trial.

239 patients, reported that PSV reduces respiratory effort compared with T-piece trial which reflected physiological conditions after extubation more accurately. However, the authors conclude that these results are tempered by the limited number of studies, the small number of patients included in each and by methodological heterogeneity.[8–23] The authors of this meta-analysis[3] stated that further investigations are therefore necessary.

To the best of our knowledge, there is no randomised cross-over trial evaluating which SBT most closely mimics postextubation effort to breathe, in a large population, in the era of modern ICU using last generation ventilators (online supplemental table S1) according to specific profiles of respiratory mechanics and critical illness.[10 17 21]

Objectives

We hypothesise that non-assisted breathing trials (PSV 0 cmH_2O PEEP 0 cmH_2O and T-piece trial) will most closely mimic effort to breathe after extubation.

Primary objective. To determine which SBT will best reproduce postextubation effort to breathe for overall patients.

Secondary objectives. To determine which SBT will best reproduce post-extubation effort to breathe for five specific critical illnesses: abdominal surgery, brain injury, chest trauma, chronic obstructive pulmonary disease (COPD) and miscellaneous.

To compare inspiratory effort at 20 min, 24 hours and 48 hours after extubation.

To compare three SBTs for effort to breath, respiratory variables and lung aeration. We will also describe the respiratory management (physiotherapy, oxygen therapy, non-invasive ventilation) following extubation, and the rate of extubation failure.

Trial design

The GLOBAL WEAN trial is an investigator initiated multicentric prospective randomised cross-over study. Each patient, serving as their own control, will perform three SBTs in a randomly assigned order. The expected duration of subject participation is 48 hours after inclusion in the study.

CONSORT diagram

Figure 1 shows the Consolidated Standards of Reporting Trial (CONSORT) diagram of the GLOBAL WEAN study.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The GLOBAL WEAN study is currently taking place in three mixed medical and surgical ICUs for a total of 52 beds, in France.

Eligibility criteria

Inclusion criteria

All consecutive ICU patients under invasive mechanical ventilation for at least 24 hours and considered by the clinician in charge to be ready for extubation according to guidelines[24] are eligible for inclusion in the study.

All criteria for ventilatory weaning must be present[24]: conscious patient (Richmond Agitation-Sedation Scale ≥0) or VISAGE (VIsual pursuit, Swallowing, Age,. Glasgow for Extubation) score ≥3[25] (visual pursuit, good swallowing, Glasgow Coma Scale >10) if severe brain injury, no sedation, good coughing effort, good swallowing, positive leak test when required (leaks ≥12% of tidal volume (VT)), no significant secretions, no respiratory acidosis, adequate oxygenation (arterial oxygen tension to inspiratory oxygen fraction ratio $(PaO_2)/FiO_2$ ≥150 mm Hg and continuous positive airway pressure ≤8), adequate pulmonary function (respiratory rate (RR) ≤35, negative inspiratory force >−20 cmH_2O, RR/VT <105), stable cardiovascular status (heart rate (HR) <140 bpm, systolic blood pressure >90 mm Hg, no or minimal vasopressors), resolution of acute phase of disease for which the patient was intubated.

Patients must be over 18 years old, have health insurance coverage and provide written consent.

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included: body mass index (BMI) (total body weight in kg/height in m^2) higher than 35 kg/m^2, any contraindication to the insertion of an oesophageal

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Figure 1 Consolidated Standards of Reporting Trial (CONSORT) diagram of the GLOBAL WEAN study. ICU, intensive care unit; SBT, spontaneous breathing trial.

catheter, age <18 years, pregnant or breastfeeding woman, protected person or under curatorship.

Critical illnesses

Five critical illnesses with specific features are defined a priori: (1) postoperative abdominal surgery with laparotomy[26] within 15 days after surgery, (2) brain injured patients,[27] (3) patients with chest trauma,[28 29] (4) COPD exacerbation according to the 2018 international guidelines,[30] (5) miscellaneous patients other than the four critical illnesses described above which could include pneumoniae, sepsis or heart failure. An ancillary study will be performed on patients with COVID-19–associated acute respiratory distress syndrome.

Outcomes

Primary outcome measure

Primary outcome will be the inspiratory effort to breathe of all inspiratory muscles evaluated by oesophageal pressure time product per minute (PTPmin). This is a reliable assessment of the patient's inspiratory effort, calculated by integration of oesophageal pressure over time.[31 32]

Measurement of oesophageal swing pressures will be performed with a second-generation balloon oesophageal catheter: Nutrivent (SIDAM, Italy), oesophageal catheter C76U (Marquat, France) and oesophageal catheter 47-9005 (CooperSurgical, Trumbull, Connecticut, USA). After insertion, the initial filling volume of inflation will be within the range defined by Mojoli *et al*[33] depending on the catheter used: 4 mL for Nutrivent and Marquat catheter, 1 mL for Cooper. Then the volume will be titrated to obtain the largest tidal oesophageal pressure (P_{es}).[34] We will confirm the appropriate position in the lower third of the oesophagus by an inspiratory effort manoeuvre performed by the patient against

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an end-expiratory occlusion. Slope of linear regression between changes in airway pressure (P_{aw}) and P_{es} should be 1±0.2 for validation of the position.[35 36] Pressures P_{aw}, P_{es} and flow will be measured with a FluxMed GrT device (L3Medical, France). Fifteen consecutive constant breathing cycles (eg, no coughing, no shallow breathing, no maximal inspiratory effort, no oesophageal spasm, no artefacts) will be assessed during the last 3 min of each period. The PTPmin will be calculated by FluxReview software (L3Medical, France). To determine the contribution of resistive or elastic workload, the oesophageal pressure time product will be also partitioned into three parts: resistive, elastic and related to the intrinsic PEEP (PEEPi) (online supplemental figure S1). Theoretical chest wall compliance required for the PTPmin is calculated using a theoretical value (4% of the predicted value for the vital capacity per cm of water) according to the manufacturers' recommendation. Even if using this theoretical value may result in approximation, this is expected to be identical for all periods and not to affect the validity of comparisons. We will use a tight-fitting facemask for the postextubation PTPmin measurements as previously described.[17 37 38]

Secondary outcome measures

Secondary outcomes will be PTPmin at 24 hours and 48 hours after extubation, changes in physiological variables and respiratory parameters at each step, postextubation respiratory management and the rate of successful extubation.

Standard three-lead monitoring electrodes will continuously record HR and rhythm. Oxygen saturation (SpO_2) will be continuously monitored using pulse oximetry. Systolic and diastolic arterial blood pressures will be continuously monitored with a non-invasive blood pressure cuff or through a 20-gauge catheter inserted in a radial or femoral artery. Arterial Blood Gases analysis (GEM Premier 3000 analyzer; Instrumentation Laboratory, Lexington, MA, USA) will be obtained at baseline and just before extubation. Central venous oxygen saturation will be collected whenever possible, when venous blood gases have been performed from a central venous catheter within 4 hours before SBT period, during SBT period and after extubation. The ventilatory variables and parameters will be collected in real time on the ventilator: inspired oxygen fraction (FiO_2), VT, RR, inspiratory flow, baseline PSV and PEEP values. After extubation, outcomes data will be collected: extubation success or failure (defined as reintubation within 48 hours) and postextubation respiratory management (physiotherapy, oxygen therapy, non-invasive ventilation).

Interventions

The experimental protocol with timeline is summarised in figure 2. A 10-minute period corresponding to a baseline state will be recorded first (using PSV and PEEP set by the clinician in charge of the patient before inclusion). Patients will be then assessed with the three SBTs: (1) PSV 7 cmH_2O and PEEP 0 cmH_2O (PSV 7 PEEP 0), (2) PSV 0 cmH_2O and PEEP 0 cmH_2O (PSV 0 PEEP 0) and (3) T-piece trial. Each patient, serving as their own control, will perform the three SBTs in a randomised order. Each SBT lasts 15 min, with a 10-minute washout period of return to baseline state between trials. Data will be recorded before (guarantee of real return to baseline) and after each SBT. In case of clinical success of the different SBTs, extubation will be decided by clinician in charge, in accordance with guidelines[24] and our local protocol described in detail in a previous review.[39] The patient will be reconnected to the ventilator with baseline parameters for 30 min before planned extubation.[40] Data will be recorded just before extubation and then 20 min, 24 hours and 48 hours after. Respiratory management after extubation is left to the discretion of attending teams and will be notified.

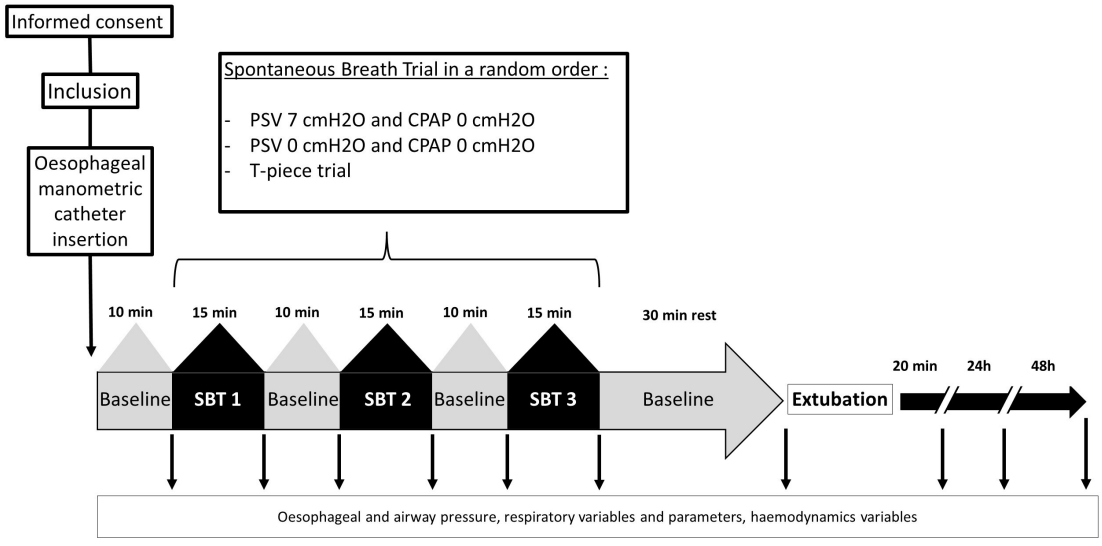


Figure 2 Study design and timeline of data collection. CPAP, continuous positive airway pressure; PSV, pressure support ventilation; SBT, spontaneous breathing trial.

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All patients will be studied in a semirecumbent position with the head of the bed elevated to an angle between 30° and 45°, according to patient comfort.[37] The humidification device is a heated humidifier, linked to a last generation ventilator from the same company (Drager, Germany). The T-piece will be connected to the inspiratory line of the ventilator and thus directly connected to the heated humidifier. The moistened air will be supplied at a flow rate of 30 L/min, with a suitable FiO_2 for SpO_2 within the targets defined by the clinician in charge.

Criteria for discontinuing or modifying allocated interventions

Patients who do not tolerate an SBT will be reconnected to the ventilator, discontinue the intervention, and therefore not be included in the data analysis. The clinician in charge will be free to perform another SBT of his choice, to extubate the patient or not.

Criteria of non-tolerance of an SBT will be:

- Excessive agitation or anxiety.
- Loss of consciousness, severe sweating and excessive end tidal carbon dioxide.
- Acute respiratory failure with RR >35 cycles per min or RR/VT>105.
- Cyanosis, dyspnoea, SpO_2<90% with FiO_2 >50%.
- Haemodynamic instability, HR >140 bpm, systolic blood pressure <80 mm Hg, high dose of vasopressors.

Strategies to improve adherence to intervention protocols

The entire procedure will be performed by the research staff, and the clinician will have no additional workload. The patient will be followed closely for 48 hours after extubation.

Relevant concomitant care and interventions that are permitted or prohibited during the trial

All care will be permitted during the procedure except for that involving additional effort for the patient: nursing, physiotherapy and painful procedure. Changes in respiratory parameters will be allowed if they are necessary for the patient (eg, FiO_2 in case of desaturation). Any changes in respiratory parameters or treatment during the procedure will be recorded.

Participant timeline

The participant timeline is described in table 2.

Sample size

To validate our hypothesis that postextubation effort to breathe will be similar to non-assisted breathing trials (PSV 0 PEEP 0 and T-piece), we plan to include up to 100 analysable patients (convenience sample according to previous physiological studies and planned subgroup analyses). We expect that we will need 120 inclusions, estimating the non-exploitable data and failed SBTs between 10% and 20% with regard to previous similar studies.[21 24] After accounting for the number of multiple comparisons, using the Bonferroni correction, significance was fixed at p<0.01.

Table 2 Participant timeline

	Screening/ baseline		Final visit
Item	**Visit 1**	**Visit 2**	**Visit 3**
Date	H0	H24	H48
Eligibility: check inclusion and exclusion criteria	X		
Informed consent	X		
Inclusion and randomisation	X		
Demography	X		
Medical history	X		
Clinical evaluation*	X	X	X
Arterial blood gases†	X	X	X
Endpoint evaluation/ physiological measures	X	X	X
Status of extubation success	X	X	X
Adverse events recording	X	X	X

*Includes haemodynamic, respiratory and ventilatory parameters.
†As usually performed for the daily patient care if an arterial catheter was in place. Supplementary blood gases could be done according to the clinical state of the patient.

Recruitment

Patients are expected to be included during a 3-year inclusion period starting June 2020.

2019: Protocol, approvals from ethics committee and trial tool development (case report form, randomisation system).

Planned start for the study: June 2020.

2020–2023: Inclusion of patients.

Planned end for the study: June 2023.

2023: Cleaning and closure of the database. Data analyses, writing of the manuscript and submission for publication.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation and sequence generation

Consecutive inclusions will be carried out in each centre. A computer-generated randomisation will be used for SBTs' order, generated by a statistician who is not involved in determining patient eligibility or outcome assessment. Randomisation will be stratified for each critical illness. Opaque sealed envelopes containing the allocation group will be then created by the statistician and addressed to the research staff. At bedside, the allocation of SBTs' order will be done by using these envelopes. The research staff will enrol participants and will assign participants to interventions.

Blinding

Patients, clinical staff (physicians, nurses, physiotherapists) and statisticians will be blind to group allocation. The blinding will not be possible for the research staff involved in the intervention. In case of non-tolerance of an SBT, the intervention will be discontinued, and the clinical staff will

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be informed. The clinician in charge will be free to perform another SBT of his choice, to extubate the patient or not.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

Data will be collected and recorded on paper case report forms by trained local research coordinators or physicians, the day of extubation, 24 and 48 hours after extubation.

Patient's characteristics will be collected and registered before intervention: age, gender, severity score quantified by Simplified Severity Index and Sequential Organ Failure Assessment Score at admission in ICU, height, weight and BMI, comorbidities (ie, pre-existing chronic respiratory disease, cardiac, renal or hepatic disease, immunosuppression) and medical or surgical ICU hospitalisation.

All original records will be kept on file for 15 years, archived in a locked room at the Intensive Care Unit & Anesthesiology Department B in University of Montpellier Saint-Eloi Hospital. The clean database file will be retained for 15 years and anonymised.

Plans to promote participant retention and complete follow-up

Not applicable. Patients will complete their intervention during their stay in the hospital.

Statistical methods

Statistical analysis

A predefined statistical analysis plan will be followed (online supplemental file 3). All analyses will be conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, V.9.4; SAS Institute; Cary, NC, USA, and R, V.3.6.2). The baseline characteristics of the overall population and of each group will be described. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with IQRs. To assess differences between SBTs and after extubation effort to breathe, we will use the Friedman test and then pairwise comparisons with the Wilcoxon test if a significant difference appears. To assess changes in physiological variables and respiratory parameters along the intervention, we will use a paired t-test. A two-sided p value of less than 0.01 will be considered to indicate statistical significance, after Bonferroni correction.

Additional analysis

A subgroup analysis will be performed to assess differences between SBTs and after extubation effort to breathe according to five illnesses: (1) abdominal surgery, (2) brain injury, (3) chest trauma, (4) COPD and (5) miscellaneous. No interim analysis will be conducted.

Analysis of non-adherence to the protocol

A per protocol analysis will be used. Patients who did not complete all three SBTs or were not extubated will not be included in the data analysis.

METHODS: MONITORING

Data monitoring

The daily patient screening and inclusion, protocol compliance, data collection and assessment are all handled by trained physicians in collaboration with a clinical research nurse and/or clinical research assistant.

Harms

The use of second-generation balloon oesophageal catheters does not appear likely to produce a significant danger during this protocol. They are already marketed and used in current clinical practice.

Concerning the project's safety, the duties of the investigator and sponsor, the reporting of major adverse events (AEs) and annual safety reports will be monitored and carried out in accordance with regulations.

Throughout the course of the study, all AEs encountered during the clinical trial will be reported continually and accurately on the AE form of the case report file. A description of the event, an evaluation of its seriousness based on the aforementioned criteria, an assessment of its duration, intensity, relationship to the study treatment, any additional causality factors (if any), any concurrent medications prescribed, actions taken with the study device or other therapeutic interventions and the outcome at the conclusion of the observation period must all be included in an AE report. A unique AE form will be filled out for each AE.

In case of major serious AEs suspected to be related to the type of SBT performed, the trial may be temporarily stopped for an individual patient, at the discretion of the attending physician.

Auditing

A midterm audit will be conducted after inclusion of 50 analysable patients. The Clinical Research and Innovation Department of the Montpellier University Hospital will be involved in this procedure independently from investigators.

Patient and public involvement statement

- Patients and public involved in the research question or the outcome measures: none.
- Patients and public involved in study design and planning: none.
- Patients and public involved in study recruitment or execution: none.
- Patients won't be the ones to judge the intervention's burden.
- Study participants will have access to results at their convenience. The results will not be systematically distributed to research participants.

ETHICS AND DISSEMINATION

Research ethics approval

The Institutional Review Board of the University Hospital of Montpellier (France) approved the trial. By 28 May 2019, the study has been approved the Ethics Committee of the Tours University Hospital (Comité de Protection

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des Personnes TOURS - Région Centre - Ouest 1, France) with the registration number 2019-A01063-54. The GLOBAL WEAN study is conducted in accordance with the Declaration of Helsinki and was registered at http://www.clinicaltrials.gov with trial identification number NCT04222569 (registered on 10 January 2020).

Plans for communicating important protocol modifications

In case of possible future protocol modifications, the Ethics Committee of the Tours University Hospital will be informed.

Consent or assent

As needed by the institutional review board in accordance with the 2013 Declaration of Helsinki, three different types of consent will be obtained (online supplemental files 4–6). The research staff will take informed consent before inclusion. After receiving written informed consent, the patient will be included. However, he may not understand given information because of brain injury. These patients will be enrolled following the next of kin's written informed consent. All patients will be retroactively prompted for written agreement to continue the trial following recovery, if possible.

Additional consent provisions for collection and use of participant data and biological specimens

Participants or their caregivers will provide further consent if related data from participants are required in future research.

Confidentiality

French legislation will be followed in the handling of data. At trial sites, all original records will be kept on file for 15 years. The clean database file will be retained for 15 years and anonymised.

Declaration of interest

The study is an investigator-initiated trial. The study promotion is performed by Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Access to data

Only the research staff and statisticians will have access to the full trial dataset during the enrolment period. The complete data collection will be available to all researchers at the end of inclusions. Controlled access will be granted to participant-level data sets. Data will be available for the corresponding author on reasonable request.

Post-trial care

We will assess, document, and treat any patients who will be harmed as a result of their involvement in the project.

Authorship eligibility, professional writers

We will not use the assistance of a professional writer.

Dissemination policy

To disseminate information and explain the research to clinicians, commissioners and service users, findings will be published in peer-reviewed journals and presented at regional, national, and worldwide meetings and conferences.

Biological specimens

Not applicable, no biological specimens will be collected.

DISCUSSION

To the best of our knowledge, GLOBAL WEAN trial will be the first pragmatic multicentric randomised physiological cross-over study with a large population, evaluating effort to breathe of three SBTs and after extubation, using the last generation of modern ICU ventilators, with a focus on specific critical illnesses (online supplemental table S1).

Online supplemental table S1 which summarises the main characteristics of 17 physiological studies evaluating different SBTs, suggests that mechanical ventilation allows to unload the respiratory muscles.[3 8–14 17 19 21] As the amount of support provided by the given SBTs' modality increases (assisted trials), the workload of patient's respiratory muscles decreases. However, there are differences in the comparison with effort to breathe after extubation. Although the landmark study by Brochard *et al*[8] showed that unassisted trials (T-piece and PSV 0) increased effort to breathe compared with postextubation, Straus *et al*[15] and Mahul *et al*[21] recorded similar respiratory effort, while Nathan *et al*,[11] Ishaaya *et al*[13] and Mehta *et al*[17] showed less effort to breathe compared with postextubation. This difference could be explained by the heterogeneity of patients, of ventilators or interfaces for postextubation assessment (mouthpiece or facemask). Performing an assisted trial helps the patient provide overall inspiratory muscle effort (resistive and elastic workload) and adds pressure needed to overcome the PEEPi. In unassisted trial, the global inspiratory muscle effort is provided by the patient. The difference that might be observed between PSV 0 PEEP 0 trial and T-piece trial could be explained by additional resistive work in PSV 0 PEEP 0 trial because, despite advances in respiratory engineering and pressurisation performance,[41–43] ventilator and circuit overload could still be significant. We might speculate that respiratory mechanism specificities and respiratory drive could be different between critical illnesses.

Strengths of the GLOBAL WEAN study are the large population comparing to other similar physiological trials, the use of last generation modern ICU ventilators and the focus on specific critical illnesses. One other strength is that the team has extensive experience in performing physiological studies about weaning, SBTs and effort to breathe evaluation, such as the WEANOBESE study[21] and others.[44–46] No industry will be involved.

Our study does present some limitations. First, the 48-hour follow-up is probably short to allow proper

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interpretation of extubation success. Second, we assumed the absence of gastric pressure measurement as previous studies did.[8 11 13 17] These missing data blind us to the participation of abdominal expiratory muscle relaxation in the initiation of the inspiratory effort. As included patients will be recovered from acute illness and ready for extubation, we considered the measurement of abdominal expiratory effort irrelevant. Third, we will not calculate the work of breathing (WOB). WOB is strongly correlated with the PTP in most physiological studies.[6] The choice of PTP as primary outcome is justified by the fact that unlike WOB, the PTP allows the assessment of non-volume-generating effort, such as the isometric load imposed by the respiratory support initiation process. Fourth, another limitation of this study is the duration of the SBT, 15 min. The standard of care is a 30-minute duration for an SBT.[47] Choosing 15 min was a deliberate decision as in previous studies,[21] in agreement with the ethics committee, in order to prevent patients' discomfort. Despite all, patient fatigue and discomfort could persist and influence performance during the trial. Random order will mitigate this, but a potential bias remains. Fifth, the total duration of the intervention will be quite long, changes in the patient's condition may appear and require care. Any changes in respiratory parameters or treatment during the procedure will be recorded. Sixth, the intervention is technical and requires a trained research staff to be available, which could be an enrolment bias and could slow down the recruitment. Seventh, the recruitment period coincides with the COVID-19 outbreak which could generate a recruitment bias. For example, the significant decrease in trauma admissions due to governments restrictions.[48 49] Eighth, some elements that may affect inspiratory effort and extubation success will not be recorded such as amount of airway secretions, percentage of leak during the cuff leak test or coughing effort (peak expiratory flow).

In conclusion, the GLOBAL WEAN study will be the first pragmatic multicentric randomised physiological cross-over study evaluating which SBT closely mimics the postextubation effort to breath, in a large population, an adequate statistical power and a considered study design, in modern era with the last generation ICU ventilators, focusing on specific critical illnesses in order to develop personalised weaning protocols as the final aim of this work.

Trial status

The trial is ongoing and is actively enrolling since June 2020.

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Funding The study is an investigator-initiated trial. Study promoter is Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Competing interests SJ reports receiving consulting fees from Drager, Mindray, Medtronic, Baxter, Fresenius-Xenios and Fisher & Paykel. ADJ reports receiving consulting fees from Drager, Medtronic and Fisher & Paykel. LB's lab has received research grants from Medtronic, Drager and Stimit and equipment from Sentec, Fisher & Paykel and Philips and lecture fees from Fisher & Paykel. No potential conflict of interest relevant to this article was reported for other authors.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Which spontaneous breathing trial to predict effort to breathe after extubation according to five critical illnesses: the cross over GLOBAL WEAN study

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Manuscript word count n = 2442 (3500 max)
Words count abstract n = 279 (250 max)
References n = 29 (30 max)
Tables n = 3
Figures n = 2
Appendix n = 10

SUMMARY

Background

Readiness to be freed from ventilatory support can be evaluated by spontaneous breathing trial (SBT) assessing the patient's ability to sustain respiratory effort after extubation. Current SBT practices are heterogenous. The objective of this study was to assess which SBT best reproduces inspiratory effort to breathe after extubation with focus on five critical illnesses.

Methods

In this multicenter randomized cross-over physiological study, adult intensive care unit patients under invasive mechanical ventilation for at least 24 hours and ready for extubation, performed three 15-minute SBTs in a random order: pressure support ventilation level of 7 cmH2O with positive end expiratory pressure level of 0 cmH2O (PSV7PEEP0), PSV 0 cmH2O with PEEP 0 cmH2O (PSV0PEEP0) and T-piece trial. Primary outcome was the pressure time product per minute (PTPmin), reflect of inspiratory effort, at baseline state, after each SBT and 20 min after extubation. Patients were divided into five categories of critical illness: abdominal surgery, brain injury, chest trauma, chronic obstructive pulmonary disease (COPD) and miscellaneous (mainly septic patients).

Findings

One hundred patients were analyzed. PTPmin (cmH2O.s/min, median and IQR) induced by unassisted trials, 291 (235-347) at the end of PSV0PEEP0 and 262 (198-338) at the end of T-piece, was similar to inspiratory effort required after extubation: 256 (208-321) (no significant difference). The assisted trial PSV7PEEP0 induced a lower inspiratory effort with 192 (127-281) ($p<0·001$). In patients with brain injury, only one SBT replicates well the postextubation effort to breathe (PSV0PEEP0), two SBTs in abdominal surgery patients (PSV0PEEP0 and T-piece) and miscellaneous patients (PSV7PEEP0 and T-piece), the three SBTs in patients with chest trauma and COPD exacerbation.

Interpretation

Unassisted SBTs, PSV0PEEP0 and T-piece trial, are the most appropriate to replicate the postextubation effort to breath.

Funding

French Society of Anesthesia and Intensive Care Medicine.

INTRODUCTION

Mechanical ventilation is a life-saving intervention and the main organ support in intensive care units (ICUs).[1] After recovery from acute illness, predicting whether a patient can be successfully liberated from ventilatory support and extubated is challenging.[2] Spontaneous breathing trials (SBT) can be performed to assess the patient's ability to sustain respiratory effort without assistance.[3]

Several SBT methods have been described, and practices are heterogeneous in ICUs. The most common SBTs are low pressure support ventilation (PSV) with or without positive end expiratory pressure (PEEP) (55%–72%) and T-piece trial (9%–59%).[4,5] A meta-analysis from Sklar et al published in 2017,[6] including 16 physiological studies and 239 patients, reported that unassisted SBT such as PSV 0 cmH2O PEEP 0 cmH2O (PSV 0 PEEP 0) and T-piece trial reflects the postextubation effort to breathe more accurately than SBT with pressure support. However, the authors conclude that these results are tempered by the limited number of studies (only 6 reported the inspiratory effort after extubation), the small sample size and by methodological heterogeneity (**Table S1**).

To the best of our knowledge, there is no multicenter randomized cross-over trial evaluating which SBT most accurately reproduces postextubation effort to breathe, in a large population, in the era of modern ICU using last generation ventilators. We aimed to determine, in these conditions, which SBT best reproduces postextubation effort to breathe, for overall patients and for five specific critical illnesses: post-operative of abdominal surgery, brain injury, chest trauma, chronic obstructive pulmonary disease (COPD) and miscellaneous. We hypothesize that unassisted SBTs, PSV 0 PEEP 0 and T-piece trial, most accurately reproduce the postextubation effort to breathe.

METHODS

Study design

We conducted an investigator initiated multicenter randomized cross-over physiological study comparing inspiratory effort throughout three SBTs and after extubation. The trial was approved for all centers by a central Ethics Committee (2019-A01063-54, Comité de Protection des Personnes TOURS - Région Centre - Ouest 1, France) according to French law. Written informed consent was required, for all patients or surrogate in case of inability to give consent. This study was registered at http://www.clinicaltrials.gov with trial identification number NCT04222569. The protocol and statistical analysis plan have been published.[7]

Participants

The trial was conducted in three mixed medical and surgical ICUs for a total of 52 beds, in France. All consecutive ICU adult patients under invasive mechanical ventilation for at least 24 hours and considered by the clinician in charge to be ready for extubation were eligible for inclusion in the study. Sedation was stopped as soon as possible.[8] Research team was blinded to eventual SBT performed by caregivers. All inclusion criteria, including guidelines criteria for ventilatory weaning,[3] are detailed in the supplementary appendix. Patients fulfilling one or more of the following criteria were not included: body mass index (BMI) higher than 35 kg/m^2, any contraindication to the insertion of an esophageal catheter, pregnant or breastfeeding woman and protected person or under curatorship.

Five critical illnesses with specific features were defined a priori: (1) postoperative abdominal surgery with laparotomy[9] within 15 days of surgery, (2) patients with brain injury,[10] (3) patients with chest trauma,[11] (4) COPD exacerbation according to international guidelines 2023,[12] (5) miscellaneous patients with other critical illnesses than those described above. An ancillary study is planned for patients with COVID-19–associated acute respiratory distress syndrome.

Procedures

The experimental protocol with timeline is summarized in **figure S1**. After informed consent, inclusion in the study, and insertion of a second-generation balloon esophageal catheter, 10 minutes of baseline state was recorded (with PSV and PEEP set by the clinician in charge prior to inclusion). Each patient, serving as their own control, performed then three 15-minute SBTs in a randomly assigned order: (1) with PSV 7 cmH2O and PEEP 0 cmH2O (PSV 7 PEEP 0), (2) PSV 0 PEEP 0 and (3) through a T-piece. A 10-minute washout period of return to baseline state was respected between trials. In case of clinical success of the different SBTs, and after a rest period of 30 minutes with baseline parameters,[13] the extubation was decided by clinician in charge, in accordance with guidelines[3] and our local protocol.[14] All patients were ventilated with a last generation Drager® ventilator. The automatic tube compensation was not used. Respiratory management after extubation was left to the discretion of attending teams and was notified. Respiratory variables (flow, volume, airway pressure and esophageal pressure) were recorded throughout baseline and SBT sessions. All data were recorded before and after each SBT, and 20 minutes after extubation.

Outcomes

The primary outcome was the inspiratory effort, assessed by esophageal pressure time product per minute (PTPmin), the integration of esophageal pressure (Pes) over time. Measurement of esophageal pressure was performed with a second-generation balloon esophageal catheter (more details in supplemental), connected to a FluxMed GrT device (L3Medical, France). Recording of airway pressure (Paw), Pes, flow (**Figure S2**), and calculation of PTPmin were performed using FluxReview software (L3Medical, France). Fifteen consecutive constant breathing cycles (e.g., no coughing, no shallow breathing, no maximal inspiratory effort, no esophageal spasm, no artefacts) from the last three minutes of each period were selected for analysis.

The secondary outcome was the swing esophageal pressure (swing Pes). Other outcomes were postextubation respiratory management (rate of chest physiotherapy, noninvasive ventilation, high flow nasal oxygenation and standard oxygenation), the rate of successful extubation at 48 hours, physiological variables and respiratory parameters.

Statistical analysis

To validate our hypothesis that inspiratory effort is similar after extubation and during unassisted breathing trials (PSV 0 PEEP 0 and T-piece), we planned to include up to 100 analyzable patients (convenience sample according to previous physiological studies and planned subgroup analyses). We expected the need of 120 inclusions, estimating the non-exploitable data and failed SBTs between 10% and 20% with regard to previous similar studies.[3,15]

All analyses were conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, V.9.4; SAS Institute; Cary, NC, USA, and R, V.4.2.1). The baseline characteristics of the overall population and of each group were described. Categorical variables were reported as frequencies and percentages and comparisons were performed with Chi-squared test. Continuous variables were reported as either means with SDs or medians with IQRs and comparisons were performed with Kruskal-Wallis rank sum test. To assess differences between SBTs and after extubation inspiratory effort, we used the Friedman test and then pairwise comparisons with the Wilcoxon test. To assess changes in physiological variables and respiratory parameters along the intervention, we used a paired t-test. A two-sided p-value of less than 0·01 was considered to indicate statistical significance in case of multiple comparisons after Bonferroni correction. A per protocol analysis was used. Patients who did not complete all three SBTs, who were not extubated and those who did not have complete postextubation inspiratory effort data were not included in the analysis.

A subgroup analysis was planned to assess differences between SBTs and after extubation effort to breathe according to five critical illnesses: (1) abdominal surgery, (2) brain injury, (3) chest trauma, (4) COPD and (5) miscellaneous.

Role of study sponsor and funding source

The sponsor has a funding and support role. This was a researcher-driven study, the funder of the study was not involved in the study's design, data collecting, data analysis, data interpretation, or report writing.

RESULTS

From June 15, 2020, to June 15, 2023, 941 ICU patients were ready for extubation after 24 hours of invasive mechanical ventilation, 104 patients were included and randomized, two failed at least one of the three SBTs, one was reintubated immediately before the 20-minute postextubation recording, and one accidentally removed the esophageal catheter. Thus 100 patients were finally analyzed (**Figure S3**) with 25 post operative of abdominal surgery, 22 patients with brain injury, 13 patients with chest trauma, 16 COPD exacerbation and 24 miscellaneous patients. The miscellaneous subgroup included nine cases of pulmonary sepsis, eight non-pulmonary sepsis, four massive hemorrhages, two heart failure and one acute respiratory failure due to myasthenia gravis. Baseline characteristics of the patients were similar between subgroups of critical illness except for age (younger patients in chest trauma subgroup, p<0·001), corticosteroids administered on the day of extubation (p<0·001) and logically comorbidities, reason for ICU admission and intubation (**Table 1**).

There were no significant differences in respiratory and hemodynamic variables between baseline, the end of the three SBT and 20 minutes after extubation (**Table 2** and **Table S2**). There was no significant difference in arterial blood gases before and after the three SBTs (**Table S2**).

For overall patients (**Figure 1** and **Figure S4**), the inspiratory effort (PTPmin and Swing Pes, median and IQR) induced by unassisted trials, 291 (235-347) cmH2O.s/min and 14·9 (11·9-19·0) cmH2O at the end of PSV 0 PEEP 0, 262 (198-338) cmH2O.s/min and 14·1 (10·0-17·4) cmH2O at the end of T-piece, was similar to inspiratory effort required after extubation: 256 (208-321) cmH2O.s/min and 14.4 (10·7-17·4) (no significant difference). The assisted trial PSV 7 PEEP 0 induced a lower inspiratory effort with 192 (127-281) cmH2O.s/min and 9.3 (6·5-13·9) cmH2O (p<0·001 in comparison with postextubation for both PTPmin and Swing Pes).

Except for postoperative abdominal surgery patients, the results differed according to critical illness (**Figure 2**, **Figure S5**, **Figure S6** and **Figure S7**). In patients with brain injury, PSV 0

PEEP 0 was the only SBT inducing no significant difference of inspiratory effort in comparison to that required after extubation. In contrast, for miscellaneous patients, PSV 0 PEEP 0 was the only SBT inducing a significant different inspiratory effort in comparison to that required after extubation. In patients with chest trauma, and COPD exacerbation, inspiratory effort induced by all three SBTs was similar to that required after extubation (no significant difference).

For overall patients, there was 6 extubation failures at 48 hours (**Table S3**). The management after extubation was similar between subgroups except for the use of noninvasive ventilation, more frequent in COPD exacerbation subgroup (p=0·018).

DISCUSSION

In this multicenter randomized cross-over physiological study, the unassisted SBTs, PSV 0 PEEP 0 and T-piece trial, most accurately reproduced the postextubation effort to breathe for overall patients. The assisted trial PSV 7 PEEP 0 underestimated the effort to breathe after extubation. The results suggest however that in patients with brain injury patients, only one SBT replicates well the postextubation effort to breathe (PSV 0 PEEP 0), two SBTs in post operative of abdominal surgery patients (PSV 0 PEEP 0 and T-piece) and miscellaneous patients (PSV 7 PEEP 0 and T-piece), the three SBTs in patients with chest trauma and COPD exacerbation. This approach to personalized weaning is in line with previously published work on personalized mechanical ventilation.[16]

Our findings are consistent with the global results presented in the meta-analysis of Sklar et al.[6] However in details there are some differences. Although the landmark study of Brochard et al.[17] showed that unassisted trials (T-piece and PSV 0 PEEP 0) increased effort to breathe in comparison to after extubation, Straus et al.[18] and Mahul et al.[15] recorded similar inspiratory effort, while Nathan et al.,[19] Ishaaya et al.,[20] and Mehta et al.[21] showed less effort to breathe in comparison to after extubation. The differences could be explained by the heterogeneity of patients, ventilators or postextubation assessment interfaces (mouthpiece or facemask). The endotracheal tube internal diameter, the amount of mucous secretions and whether or not a humidification device is used (especially in the T-piece trial), are other factors which could affect the effort to breathe. Persistent high inspiratory effort after extubation may also result from upper airway edema or inflammation, which could be mitigated by corticosteroids administration. A multicenter study on a large population with a unique standardized methodology was necessary.

We might speculate that the differences in results between critical illnesses could be explained by respiratory specificities. Post operative of abdominal surgery patients present a restrictive rather than obstructive profile which could explain the similarity between unassisted SBTs and

postextubation effort to breathe (low proportion of resistive workload induced by endotracheal tube and ventilator circuit). The abdominal distension decreases the pulmonary vital capacity and alters chest wall mechanics.[22,23] Patients with brain injury mainly present upper airway's dysfunction[4] with elevation of pharyngeal collapsibility and airway resistance, which could explain the significant effort to breathe after extubation. Moreover, in our population, few patients in this subgroup received systemic corticosteroids on the day of extubation. Patients with chest trauma have an alteration of chest wall compliance[24] and a restrictive profile similar to that of post operative of abdominal surgery patients. The limited population of this subgroup may explain the absence of significant difference between PSV 7 PEEP 0 and after extubation effort to breath (p=0·08, versus p=0·38 for PSV 0 PEEP 0 and p=0·54 for T-piece). COPD patients have obstructive profile with high resistive workload, and despite of theorical adapted endotracheal tube size (no patient with endotracheal tube internal diameter less to 7·5 mm in our population), these patients benefit from a low level of PSV for an optimal SBT.[17] Miscellaneous patients, which are essentially septic patients, present mixed profile. We need to be cautious with these inflammatory patients, who present a high risk of diaphragm impairment,[25] especially with SBTs inducing high workload.[26]

Conducting a physiological study with respiratory effort assessment is technically challenging and the main strength of the GLOBAL WEAN study is its large sample size compared with other similar trials, permitting focus on specific critical illnesses. Our study presents however some limitations. First, we assumed the absence of gastric pressure measurement. This missing data blind us to the participation of abdominal expiratory muscle relaxation in the initiation of the inspiratory effort. As included patients will be recovered from acute illness and ready for extubation, we considered the measurement of abdominal expiratory effort irrelevant. We also did not calculate the work of breathing, which is strongly correlated with the PTP.[6] We chose the PTP as primary outcome because it allows the assessment of non-volume-generating effort, such as the isometric load imposed by the respiratory support initiation process. Secondly, the 48-hour follow-up is probably short to allow proper interpretation of

clinical outcomes such as extubation success or the impact of post extubation respiratory management. This was not the main objective of our physiological study and other randomized controlled trials have answered these questions.[27,28] Thirdly, the recruitment period coincided with the COVID-19 outbreak which could generate a recruitment bias. For example, the significant decrease in trauma admissions due to governments restrictions.[29]

In summary, in this multicenter randomized cross-over physiological study, we have shown that unassisted SBTs, PSV 0 PEEP 0 and T-piece trial, are the most appropriate to replicate the postextubation effort to breath, moreover in patients with brain injury, with some caution in septic patients. Further studies are needed to explain more accurately the differences between critical illnesses.

Table 1. Baseline characteristics of the participants

	Overall (n=100)	Abdominal surgery (n=25)	Brain injury (n=22)	Chest trauma (n=13)	COPD (n=16)	Misc (n=24)
Age, years	61 (15)	66 (13)	58 (15)	44 (17)	68 (8)	65 (12)
Male sex	60 (60%)	15 (60%)	13 (59%)	10 (77%)	6 (38%)	16 (67%)
BMI at admission, kg/m²	26 (4·9)	26 (5)	25 (4)	26 (4)	24 (5)	26 (6)
SAPS II at admission	61 (18)	59 (16)	66 (19)	49 (17)	63 (20)	62 (15)
SOFA score at admission	10 (4)	10 (3)	11 (5)	8 (4)	9 (4)	10 (4)
Comorbidities						
Alcohol abuse	32 (32%)	7 (28%)	7 (32%)	1 (7·7%)	6 (38%)	11 (46%)
Active smoking	43 (43%)	9 (36%)	9 (41%)	2 (15%)	13 (81%)	10 (42%)
Psychotropic treatment	37 (37%)	7 (28%)	11 (50%)	3 (23%)	9 (56%)	7 (29%)
Obesity with BMI > 30	26 (26%)	9 (36%)	4 (18%)	4 (31%)	3 (19%)	6 (25%)
Diabetes	16 (16%)	4 (16%)	3 (14%)	0 (0%)	4 (25%)	5 (21%)
Systemic hypertension	34 (34%)	10 (40%)	6 (27%)	0 (0%)	8 (50%)	10 (42%)
Coronary disease	17 (17%)	3 (12%)	4 (18%)	0 (0%)	4 (25%)	6 (25%)
Cardiac insufficiency	6 (6%)	1 (4·0%)	1 (4·5%)	0 (0%)	0 (0%)	4 (17%)
Chronic renal failure	8 (8%)	5 (20%)	1 (4·5%)	0 (0%)	0 (0%)	2 (8·3%)
Cirrhosis	21 (21%)	7 (28%)	5 (23%)	0 (0%)	2 (12%)	7 (29%)
Chronic respiratory failure	5 (5%)	1 (4·0%)	0 (0%)	0 (0%)	3 (19%)	1 (4·2%)
COPD	22 (22%)	4 (16%)	0 (0%)	0 (0%)	16 (100%)	2 (8·3%)
Immunocompromised	9 (9%)	2 (8·0%)	3 (14%)	0 (0%)	0 (0%)	4 (17%)
Main reason for ICU admission						
Post operative	23 (23%)	21 (84%)	1 (4·5%)	0 (0%)	1 (6·2%)	0 (0%)
Cardiac arrest	2 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (6·2%)	1 (4·2%)
Sepsis	10 (10%)	1 (4·0%)	0 (0%)	0 (0%)	3 (19%)	6 (25%)
Coma	9 (9%)	0 (0%)	9 (41%)	0 (0%)	0 (0%)	0 (0%)
Trauma	20 (20%)	0 (0%)	8 (36%)	12 (92%)	0 (0%)	0 (0%)
Acute respiratory failure	23 (23%)	0 (0%)	0 (0%)	1 (7·7%)	11 (69%)	11 (46%)
ALF or ACLF	5 (5%)	1 (4·0%)	2 (9·1%)	0 (0%)	0 (0%)	2 (8·3%)
Massive hemorrhage	8 (8%)	2 (8·0%)	2 (9·1%)	0 (0%)	0 (0%)	4 (17%)
Main reason for intubation						
Before procedure*	37 (37%)	23 (92%)	3 (14%)	6 (46%)	1 (6·2%)	4 (17%)
Cardiac arrest	2 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (6·2%)	1 (4·2%)
Shock	13 (13%)	2 (8%)	0 (0%)	0 (0%)	3 (19%)	8 (33%)
Coma	19 (19%)	0 (0%)	19 (86%)	0 (0%)	0 (0%)	0 (0%)
Acute respiratory failure	29 (29%)	0 (0%)	0 (0%)	7 (54%)	11 (69%)	11 (46%)
Extubation failure prior to randomization†	12 (12%)	4 (16%)	1 (4·5%)	1 (7·7%)	0 (0%)	6 (25%)
Length of invasive mechanical ventilation before extubation, days	7 (7)	6 (7)	9 (6)	9 (8)	7 (8)	7 (6)
Systemic corticosteroids administered the day of extubation	40 (40%)	17 (68%)	2 (9·1%)	0 (0%)	9 (56%)	12 (50%)
ETT internal diameter, mm						
6.5	1 (1%)	1 (4·0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
7	11 (11%)	2 (8·0%)	5 (23%)	2 (15%)	0 (0%)	2 (8·3%)
7.5	50 (50%)	16 (64%)	7 (32%)	5 (38%)	10 (62%)	12 (50%)
8	32 (32%)	4 (16%)	8 (36%)	6 (46%)	6 (38%)	8 (33%)
8.5	5 (5%)	1 (4·0%)	2 (9·1%)	0 (0%)	0 (0%)	2 (8·3%)
9	1 (1%)	1 (4·0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Data are presented in n (%) and mean (SD). Significant difference for age (p<0·001, Kruskal-Wallis rank sum test) and for corticosteroids administered (p<0·001, Chi-squared test). COPD=chronic obstructive pulmonary disease. Misc=Miscellaneous. BMI=Body Mass Index. SAPS=Simplified Acute Physiologic Score. SOFA=Sequential Organ Failure Assessment. ICU=Intensive Care Unit. ALF=Acute Liver Failure. ACLF=Acute on Chronic Liver Failure. ETT=Endotracheal Tube. *Before procedure denoted that patients were intubated for a procedure, surgical or endoscopic. †Defined by reintubation within 7 days of extubation.

Table 2. Respiratory and hemodynamic variables at baseline, at the end of the three spontaneous breathing trial and 20 minutes after extubation.

	Baseline	PSV7-PEEP0	PSV0-PEEP0	TPiece	After Extubation
SpO_2, %	97 (2)	96 (3)	96 (3)	95 (3)	98 (3)
RR, breaths/min	21 (6)	21 (7)	23 (7)	22 (6)	22 (6)
$EtCO_2$, mmHg	34 (7)	34 (7)	35 (8)	..	..
V_T, mL	462 (130)	475 (133)	471 (125)	..	..
RR/V_T, min/mL	49 (21)	50 (22)	53 (25)	..	..
V_E, L/min	9 (3)	9 (3)	9 (3)	..	..
NIF*, cmH_2O	29 (11)	29 (11)	30 (10)	..	..
$P_{0.1}$*, cmH2O	2 (2)	2 (2)	3 (3)	..	..
HR, beats/min	83 (20)	86 (20)	88 (19)	88 (21)	89 (21)
SBP, mmHg	127 (21)	131 (22)	136 (21)	133 (21)	135 (22)
DBP, mmHg	62 (11)	64 (11)	66 (12)	64 (12)	65 (12)
MBP, mmHg	85 (13)	87 (14)	90 (16)	88 (14)	89 (17)

Data are presented in mean (SD). *Absolute value. PSV=Pressure Support Ventilation. PEEP=Positive End Expiratory Pressure. SpO_2=Pulse oximetry. RR=Respiratory Rate. $EtCO_2$=End tidal carbon dioxide. V_T=Tidal volume. V_E=Minute ventilation. NIF=Negative Inspiratory Force. $P_{0.1}$=Negative airway pressure generated during the first 100 msec of an occluded inspiration. HR=Heart Rate. SBP=Systolic Blood Pressure. DBP=Diastolic Blood Pressure. MBP=Mean Blood Pressure.

Table 3: Strength of inspiratory effort similarities between each spontaneous breathing trial and after extubation.

	PSV7-PEEP0	PSV0-PEEP0	TPiece
Overall (n=100)	+	+++	+++
Abdominal surgery (n=25)	+	+++	+++
Brain injury (n=22)	+	+++	+
Chest trauma (n=13)	++	++	+++
COPD (n=16)	+++	+++	+++
Miscellaneous (n=24)	+++	+	+++

+++: spontaneous breathing trial providing effort to breathe strongly similar to that provided after extubation with a non-significant difference and a median value of pressure time product per minute in the interquartile range 25%-75% of post extubation pressure time product per minute.

++: spontaneous breathing trial providing effort to breathe moderately similar to that provided after extubation with a non-significant difference and a median value of pressure time product per minute outside the interquartile range 25%-75% of post extubation pressure time product per minute.

+: spontaneous breathing trial providing effort to breathe slightly similar to that provided after extubation with a significant difference ($p<0{\cdot}01$).

PSV=Pressure Support Ventilation. PEEP=Positive End Expiratory Pressure

FIGURES LEGEND

Figure 1: (A) Pressure time product per minute (PTPmin) and (B) esophageal pressure swing (Swing Pes) obtained at baseline, at the end of the three spontaneous breathing trials and 20 minutes after extubation for overall analyzed patients.

(A) Pressure time product (PTPmin) and (B) Esophageal swing pressure (Swing Pes) of overall patients (n=100 patients) obtained after 10 minutes of baseline ventilation, after 15 minutes of spontaneous breathing trial (SBT) with pressure support ventilation (PSV) of 7 cmH_2O without positive end expiratory pressure (PEEP), after 15 minutes of SBT without PSV (0 cmH_2O) without PEEP, after 15 minutes of SBT with T-piece (only oxygenation without assistance) and 20 minutes after extubation.

NS=non-significant difference (p>0·01, Wilcoxon signed rank test)

Figure 2: Pressure time product per minute (PTPmin) obtained at baseline, at the end of the three spontaneous breathing trials and 20 minutes after extubation according to the five phenotypes of patients: (A) post operative of abdominal surgery, (B) brain injury, (C) chest trauma, (D) chronic obstructive pulmonary disease (COPD) exacerbation and (E) miscellaneous patients.

Pressure time product (PTPmin) of (A) post operative of abdominal surgery patients (n=25 patients), (B) patients with brain injury (n=22 patients), (C) patients with chest trauma (n=13 patients), (D) patients with chronic obstructive pulmonary disease (COPD) exacerbation (n=16 patients) and (E) miscellaneous patients (n=24 patients) obtained after 10 minutes of baseline ventilation, after 15 minutes of spontaneous breathing trial (SBT) with pressure support ventilation (PSV) of 7 cmH_2O without positive end expiratory pressure (PEEP), after 15 minutes of SBT without PSV (0 cmH_2O) without PEEP, after 15 minutes of SBT with T-piece (only oxygenation without assistance) and 20 minutes after extubation.

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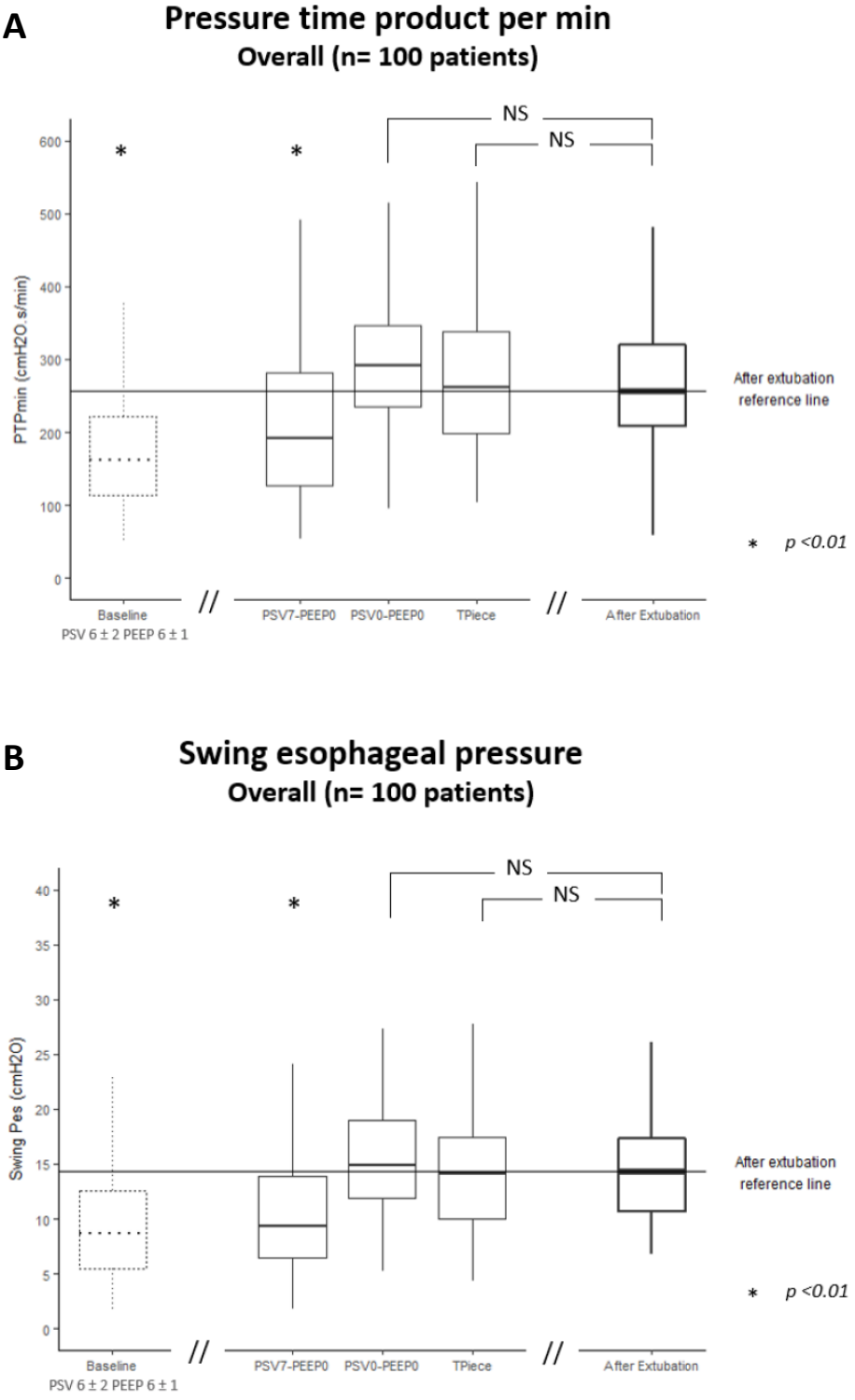
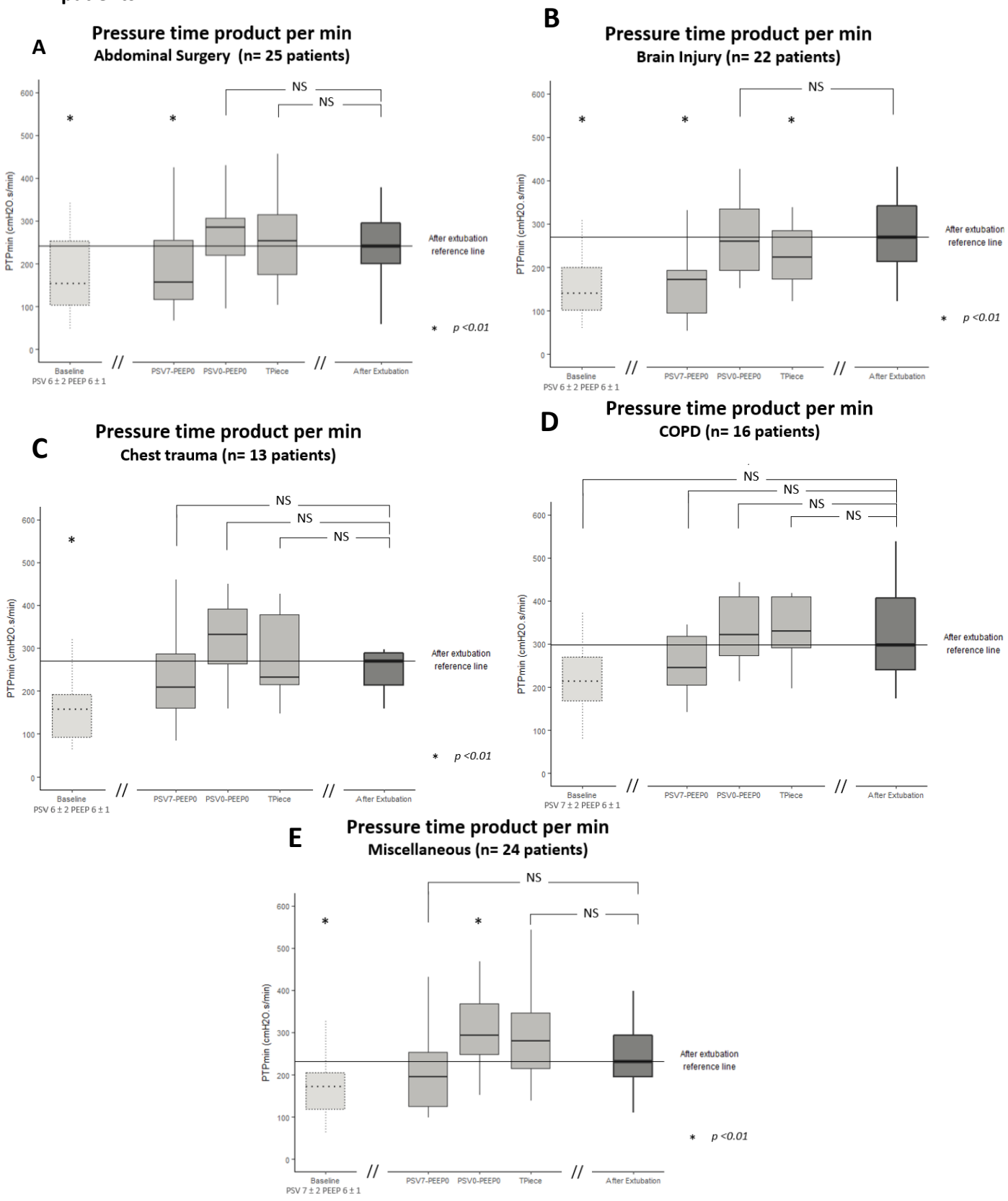


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Which spontaneous breathing trial to predict effort to breathe after extubation according to five critical illnesses: the cross over GLOBAL WEAN study

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Figure S7: Esophageal pressure swing (Swing Pes) obtained at baseline, at the end of the three spontaneous breathing trials and 20 minutes after extubation according to the five phenotypes of patients including outliers: (A) post operative of abdominal surgery, (B) brain injury, (C) chest trauma, (D) chronic obstructive pulmonary disease (COPD) exacerbation and (E) miscellaneous patients.

3. SUPPLEMENTAL REFERENCES

METHODS

Participants:

The trial was conducted in three mixed medical and surgical intensive care units (ICU) for a total of 52 beds, in France. The first center was the Department of Anesthesiology and Critical Care Medicine B (DAR B), Saint-Eloi Hospital, University Teaching Hospital of Montpellier in France, opened in June 2020. The second center was the Department of Anesthesiology and Critical Care Medicine A (DAR A), Lapeyronie Hospital, University Teaching Hospital of Montpellier in France, opened in January 2021. The third center was the critical care unit of the Clinique Saint Jean private hospital, Saint Jean de Vedas in France, opened in March 2021.

All consecutive ICU adult patients under invasive mechanical ventilation for at least 24 hours and considered by the clinician in charge to be ready for extubation were eligible for inclusion in the study. Sedation was stopped as soon as possible.[1] Research team was blinded to eventual spontaneous breathing trial (SBT) performed by caregivers. All criteria for ventilatory weaning had to be present:[2] conscious patient (Richmond Agitation-Sedation Scale ≥0) or VISAGE (VIsual pursuit, Swallowing, Age, Glasgow for Extubation) score ≥3 (visual pursuit, good swallowing, Glasgow Coma Scale >10) if severe brain injury,[3] no sedation, good coughing effort, good swallowing, positive leak test when required (leaks ≥12% of tidal volume (VT)), no significant secretions, no respiratory acidosis, adequate oxygenation (arterial oxygen tension to inspiratory oxygen fraction ratio (PaO2)/FiO2 ≥150 mm Hg and continuous positive airway pressure ≤8), adequate pulmonary function (respiratory rate (RR) ≤35, negative inspiratory force >−20 cmH2O, RR/VT <105), stable cardiovascular status (heart rate (HR) <140 bpm, systolic blood pressure >90 mm Hg, no or minimal vasopressors), resolution of acute phase of disease for which the patient was intubated. Patients had health insurance coverage and provided written consent.

Patients fulfilling one or more of the following criteria were not included: body mass index (BMI) higher than 35 kg/m^2, any contraindication to the insertion of an esophageal catheter, pregnant or breastfeeding woman and protected person or under curatorship.

Five critical illnesses with specific features were defined a priori: (1) postoperative abdominal surgery with laparotomy[4] within 15 days of surgery, (2) patients with brain injury,[5] (3) patients with chest trauma,[6] (4) chronic obstructive pulmonary disease (COPD) exacerbation according to international guidelines 2023,[7] (5) miscellaneous patients with other critical illnesses than those described above. An ancillary study is planned for patients with COVID-19–associated acute respiratory distress syndrome.

Procedures:

The experimental protocol with timeline is summarized in **figure S1**. After informed consent and inclusion in the study, the insertion of a second-generation balloon esophageal catheter was performed: Nutrivent (SIDAM, Italy), esophageal catheter C76U (Marquat, France) and esophageal catheter 47-9005 (CooperSurgical, Trumbull, Connecticut, USA). Ten minutes of baseline state was recorded with pressure support ventilation (PSV) and positive end expiratory pressure (PEEP) set by the clinician in charge prior to inclusion. Each patient, serving as their own control, performed then three 15-minute spontaneous breathing trials in a randomly assigned order: (1) with PSV 7 cmH2O and PEEP 0 cmH2O (PSV 7 PEEP 0), (2) PSV 0 PEEP 0 and (3) through a T-piece. A 10-minute washout period of return to baseline state was respected between trials. In case of clinical success of the different SBTs, and after a rest period of 30 minutes with baseline parameters,[8] the extubation was decided by clinician in charge, in accordance with guidelines[2] and our local protocol.[9] All patients were ventilated with a last generation Drager® ventilator: Drager Evita XL®, Drager Infinity Evita V500®, Drager Evita V600® and Drager Evita V800®. The automatic tube compensation was not used. Respiratory management after extubation was left to the discretion of attending teams and was notified. Respiratory variables (flow, volume, airway pressure and esophageal pressure) were recorded throughout baseline and SBT sessions with the with a FluxMed GrT device

(L3Medical, France). All data were recorded before and after each SBT, and 20 minutes after extubation. All patients were studied in a semirecumbent position with the head of the bed elevated to an angle between 30° and 45°, according to patient comfort.[10] The humidification device was a heated humidifier, linked to a last generation ventilator from the same company (Drager, Germany). The T-piece was connected to the inspiratory line of the ventilator and thus directly connected to the heated humidifier. The moistened air was supplied at a flow rate of 30 L/min, with a suitable FiO2 for SpO2 within the targets defined by the clinician in charge.

Patients who did not tolerate an SBT were reconnected to the ventilator, discontinued the intervention, and therefore not be included in the data analysis. The clinician in charge was free to perform another SBT of his choice, to extubate the patient or not. Criteria of non-tolerance of an SBT were excessive agitation or anxiety, loss of consciousness, severe sweating and excessive end tidal carbon dioxide, acute respiratory failure with RR >35 cycles per min or RR/VT>105, cyanosis, dyspnea, SpO2<90% with FiO2 >50%, hemodynamic instability, HR >140 bpm, systolic blood pressure <80 mm Hg, high dose of vasopressors.

Outcomes:

The primary outcome was the inspiratory effort, assessed by esophageal pressure time product per minute (PTPmin), the integration of esophageal pressure (Pes) over time. Measurement of esophageal pressure was performed with a second-generation balloon esophageal catheter, connected to a FluxMed GrT device (L3Medical, France). After insertion, the initial filling volume of inflation was within the range defined by Mojoli et al[11] depending on the catheter used: 4 mL for Nutrivent and Marquat catheter, 1 mL for Cooper. Then the volume was titrated to obtain the largest tidal esophageal pressure (Pes).[12] We confirmed the appropriate position in the lower third of the esophagus by an inspiratory effort maneuver performed by the patient against an end-expiratory occlusion. Slope of linear regression between changes in airway pressure (Paw) and Pes should be 1±0.2 for validation of the position.[13,14] Pressures Paw, Pes and flow (**Figure S2**) will be measured with a FluxMed GrT device (L3Medical, France). Fifteen consecutive constant breathing cycles (eg, no coughing,

no shallow breathing, no maximal inspiratory effort, no oesophageal spasm, no artefacts) will be assessed during the last 3 min of each period. The PTPmin will be calculated by FluxReview software (L3Medical, France). Theoretical chest wall compliance required for the PTPmin is calculated using a theoretical value (4% of the predicted value for the vital capacity per cm of water) according to the manufacturers' recommendation. Even if using this theoretical value may result in approximation, this is expected to be identical for all periods and not to affect the validity of comparisons. We will use a tight-fitting facemask for the postextubation PTPmin measurements as previously described.[10,15,16]

The secondary outcome was the swing esophageal pressure (swing Pes). Other outcomes were postextubation respiratory management (rate of chest physiotherapy, noninvasive ventilation, high flow nasal oxygenation and standard oxygenation), the rate of successful extubation at 48 hours, physiological variables and respiratory parameters : systolic (SBP), diastolic (DBP) and mean (MBP) arterial blood pressures, heart rate (HR), oxygen saturation (SpO_2), respiratory rate (RR), end-tidal carbon dioxide ($EtCO_2$), tidal volume (V_T), minute ventilation (V_E), negative inspiratory force (NIF), negative airway pressure generated during the first 100 msec of an occluded inspiration ($P_{0.1}$) and arterial blood gases analysis.

Data collection and management

Data were collected and recorded on paper case report forms by trained local research coordinators or physicians, the day of extubation. Patient's characteristics were collected and registered before intervention: age, gender, severity score quantified by Simplified Severity Index and Sequential Organ Failure Assessment Score at admission in ICU, height, weight and body mass index (BMI), comorbidities (ie, pre-existing chronic respiratory disease, cardiac, renal or hepatic disease, immunosuppression) and medical or surgical ICU hospitalization. All original records will be kept on file for 15 years, archived in a locked room at the Intensive Care Unit & Anesthesiology Department B in University of Montpellier Saint-Eloi Hospital. The clean database file will be retained for 15 years and anonymized.

Table S1: Characteristics of 17 physiologic studies evaluating spontaneous breathing trials.

References	Sample Size (n patients)	Population	Outcomes	Evaluation of two SBTs	Evaluation of three SBTs	Evaluation of effort to breathe after extubation	Randomized cross over trials	Multicentric	Use of last generation ventilator
Brochard et al. 1991[17]	11	Non selected	WOB, RR/V_T	**Yes**	**Yes**	**Yes**	No	No	No
Sassoon et al. 1991[18]	10	Non selected	PTP, RR/V_T	**Yes**	**Yes**	No	**Yes**	No	No
Sassoon et al. 1992[19]	9	COPD	WOB	**Yes**	**Yes**	No	**Yes**	No	No
Nathan et al. 1993[20]	7	Non selected	WOB, PTP, RR/V_T	**Yes**	**Yes**	**Yes**	No	No	No
Petros et al. 1993[21]	8	Non selected	WOB, PTP, RR/V_T	**Yes**	**Yes**	No	No	No	No
Ishaaya et al. 1995[22]	8	Non selected	WOB, PTP, RR/V_T	**Yes**	**Yes**	**Yes**	No	No	No
Patel et al. 1996[23]	23	Non selected	WOB, PTP, RR/V_T	**Yes**	**Yes**	No	No	No	No
Straus et al. 1998[24]	14	Non selected	WOB, RR/V_T	**Yes**	No	**Yes**	No	No	No
Koh et al. 2000[25]	44	Non selected	WOB, PTP, RR/V_T	**Yes**	No	No	**Yes**	No	No
Mehta et al. 2000[15]	20	Hypoxemic	WOB, PTP, RR/V_T	**Yes**	**Yes**	**Yes**	**Yes**	No	No
Kuhlen et al. 2003[26]	12	Non selected	WOB, PTP, RR/V_T	**Yes**	**Yes**	No	**Yes**	No	No
Cabello et al. 2010[27]	14	Non selected	WOB, PTP, RR/V_T	**Yes**	**Yes**	No	**Yes**	No	No
Muttini et al. 2015[28]	18	Non selected	EAdi	**Yes**	No	No	No	No	No
Mahul et al. 2016[29]	17	Obese	WOB, PTP, RR/V_T	**Yes**	**Yes**	**Yes**	**Yes**	No	**Yes**
Ferreira et al. 2017[30]	20	Non selected	EAdi	**Yes**	No	No	**Yes**	No	No
Guerin et al. 2019[31]	20	Non selected	WOB	**Yes**	No	No	**Yes**	No	**Yes**
Current study	100	COPD Chest trauma Brain injury Abdominal surgery	PTP	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**

SBT=Spontaneous Breathing Trial. COPD=Chronic Obstructive Pulmonary Disease. WOB=Work of Breathing. RR=Respiratory Rate. V_T=Tidal Volume. PTP=Pressure Time Product. EAdi=Electrical activity of the diaphragm.

Table S2: Arterial blood gases, respiratory and hemodynamic variables at each consecutive step of the study.

	Baseline 1	SBT 1	Baseline 2	SBT 2	Baseline 3	SBT 3	Baseline 4	Post extubation
pH	7·45 (0·05)	--	--	--	--	--	7·45 (0·06)	--
$PaCO_2$, mmHg	39 (12)	--	--	--	--	--	38 (8)	--
Bicarbonates, mmol/L	26 (5)	--	--	--	--	--	26 (5)	--
PaO_2/FiO_2	293 (111)	--	--	--	--	--	292 (154)	--
SpO_2, %	97 (2)	95 (10)	96 (10)	96 (3)	95 (12)	96 (3)	97 (3)	98 (3)
RR, breaths/min	21 (6)	22 (7)	21 (6)	22 (7)	21 (6)	22 (7)	21 (7)	22 (6)
$EtCO_2$, mmHg	34 (7)	34 (8)	34 (7)	34 (7)	34 (7)	34 (7)	34 (7)	--
V_T, mL	462 (130)	475 (122)	479 (128)	475 (130)	464 (110)	477 (122)	471 (129)	--
RR/V_T, min/mL	49 (21)	49 (21)	47 (20)	50 (21)	48 (20)	50 (24)	49 (22)	--
V_E, L/min	9 (3)	9 (3)	9 (3)	9 (3)	9 (3)	9 (3)	10 (8)	--
NIF*, cmH_2O	29 (11)	29 (10)	29 (11)	30 (11)	28 (11)	30 (11)	28 (11)	--
$P_{0.1}$*, cmH2O	2 (2)	2 (2)	2 (2)	3 (2)	2 (2)	3 (3)	2 (2)	--
HR, beats/min	83 (20)	87 (20)	85 (20)	87 (21)	86 (21)	88 (19)	88 (23)	89 (21)
SBP, mmHg	127 (21)	131 (22)	130 (20)	133 (21)	131 (21)	136 (21)	135 (21)	135 (22)
DBP, mmHg	62 (11)	64 (12)	63 (11)	64 (11)	65 (12)	65 (12)	65 (12)	65 (12)
MBP, mmHg	85 (13)	87 (13)	87 (13)	89 (14)	88 (14)	89 (17)	89 (16)	89 (17)

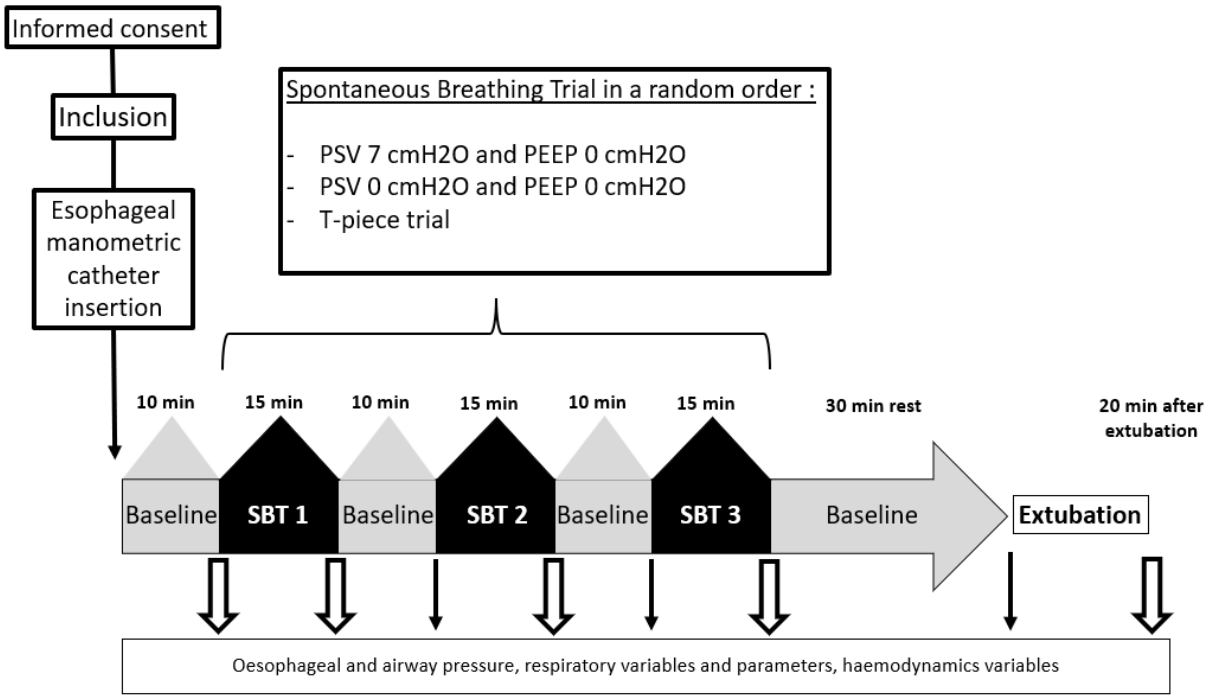
Data are presented in mean (SD). *Absolute value. SBT=Spontaneous Breathing Trial. $PaCO_2$=arterial partial pressure of carbon dioxide. PaO_2/FiO_2=arterial partial pressure of oxygen over inspired fraction of oxygen. SpO_2=Pulse oximetry. RR=Respiratory Rate. $EtCO_2$=End tidal carbon dioxide. V_T=Tidal volume. V_E=Minute ventilation. NIF=Negative Inspiratory Force. $P_{0.1}$=Negative airway pressure generated during the first 100 msec of an occluded inspiration. HR=Heart Rate. SBP=Systolic Blood Pressure. DBP=Diastolic Blood Pressure. MBP=Mean Blood Pressure.

Table S3: Post extubation management and rate of extubation failure at 48 hours.

	Overall (n=100)	Abdominal surgery (n=25)	Brain injury (n=22)	Chest trauma (n=13)	COPD (n=16)	Misc (n=24)
Post extubation management						
Chest physiotherapy	46 (46%)	8 (32%)	14 (64%)	7 (54%)	7 (44%)	10 (42%)
Noninvasive ventilation	10 (10%)	2 (8·0%)	0 (0%)	0 (0%)	5 (31%)	3 (12%)
High flow nasal oxygenation	66 (66%)	17 (68%)	12 (55%)	9 (69%)	10 (62%)	18 (75%)
Standard oxygenation	22 (22%)	6 (24%)	8 (36%)	3 (23%)	1 (6·2%)	4 (17%)
No oxygenation	5 (5·0%)	1 (4·0%)	2 (9·1%)	1 (7·7%)	1 (6·2%)	0 (0%)
Extubation failure at 48 hours*	6 (6%)	0 (0%)	0 (0%)	1 (7·7%)	2 (12·5%)	3 (12·5%)

Data are presented in n (%). COPD=chronic obstructive pulmonary disease. Misc=Miscellaneous. *Defined by reintubation within 48 hours of extubation.

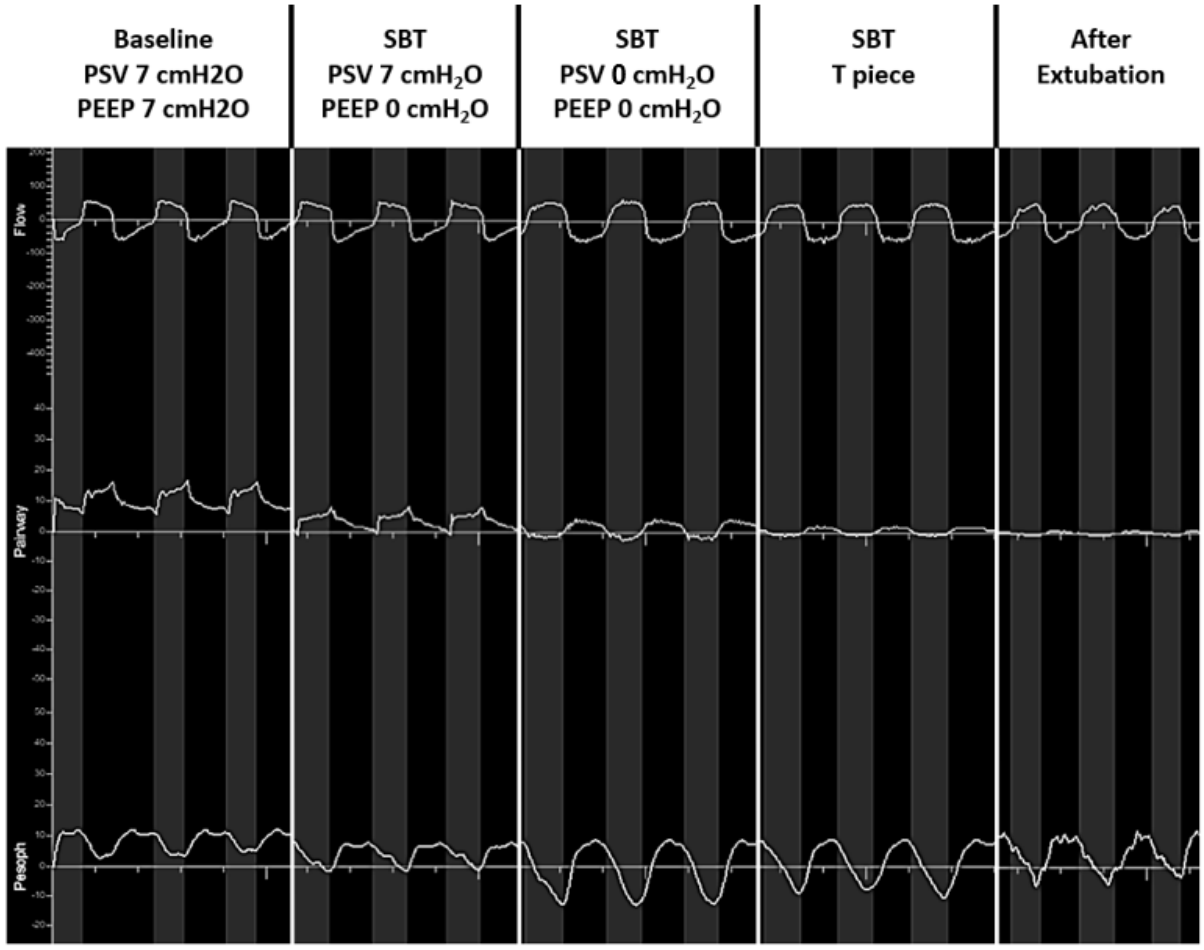
Figure S1: Study design



After informed consent, inclusion in the study, insertion of a second-generation balloon esophageal catheter, and after 10 minutes of baseline, three 15-minute spontaneous breathing trials (SBTs) were performed in a randomized order, with a 10-minute washout period of return to baseline state between trials. In case of clinical success of the different SBTs, and after a rest period of 30 minutes, the extubation was decided by clinician in charge. Respiratory variables (flow, volume, airway pressure and esophageal pressure) were recorded throughout baseline and SBT sessions. Arrows indicate recording points for all data. Bold white arrows indicate the main recording points (illustrated in figure 1, figure 2, figure S3-7).

PSV=Pressure Support Ventilation. PEEP=Positive End Expiratory Pressure. SBT=Spontaneous Breathing Trial.

Figure S2: Illustrative ventilatory pattern of a post operative of abdominal surgery patient.



Illustrative ventilatory pattern of a post operative of abdominal surgery patient at baseline, at the end of the three 15-minute spontaneous breathing trials and 20 minutes after extubation. Flow (L/s), airway pressure (Pairway, cmH2O) and esophageal pressure (Pesoph, cmH2O) were recorded with FluxReview® software (L3Medical, France).

SBT=Spontaneous Breathing Trial. PSV=Pressure Support Ventilation. PEEP=Positive End Expiratory Pressure.

Figure S3: Flow chart

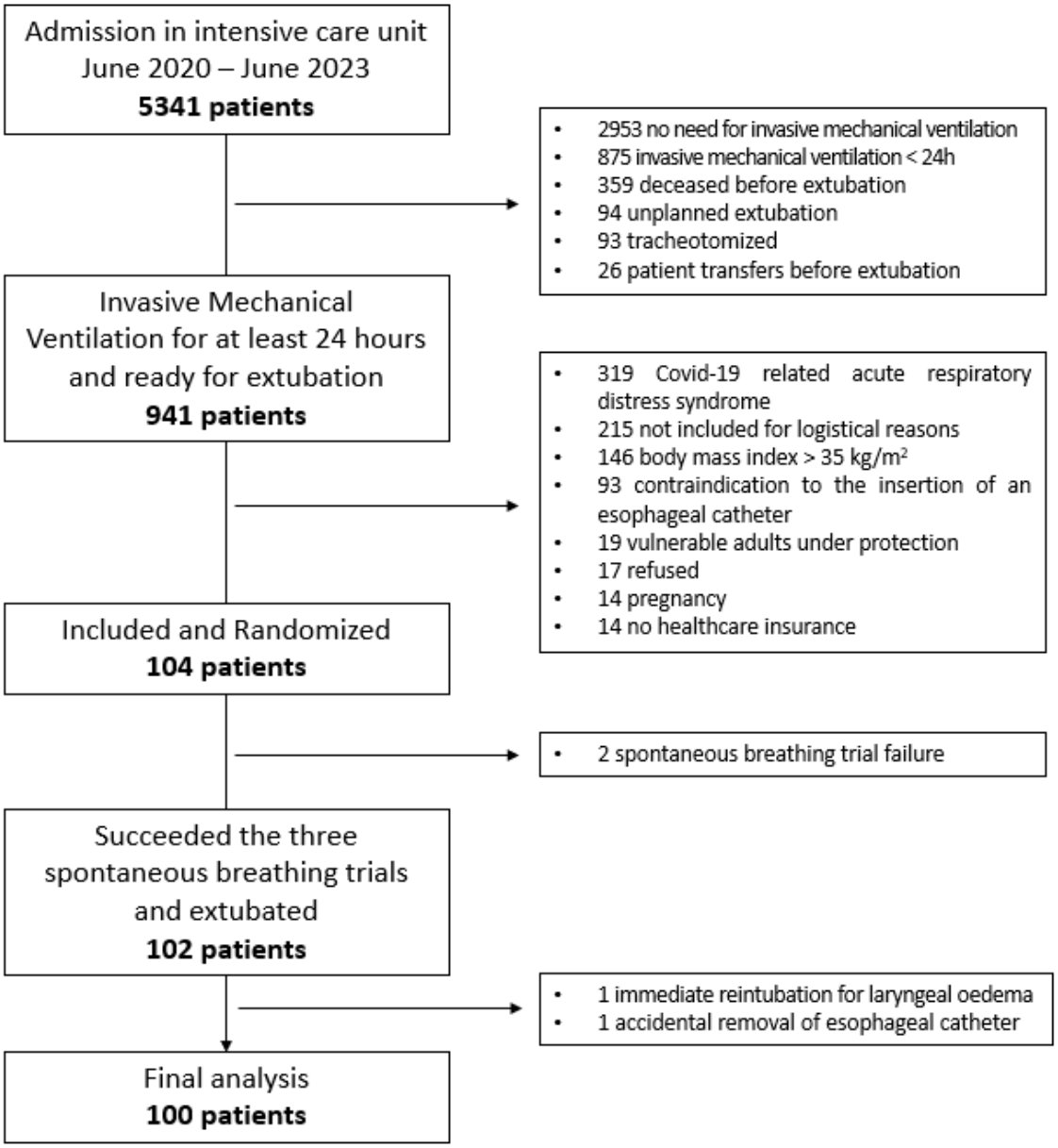
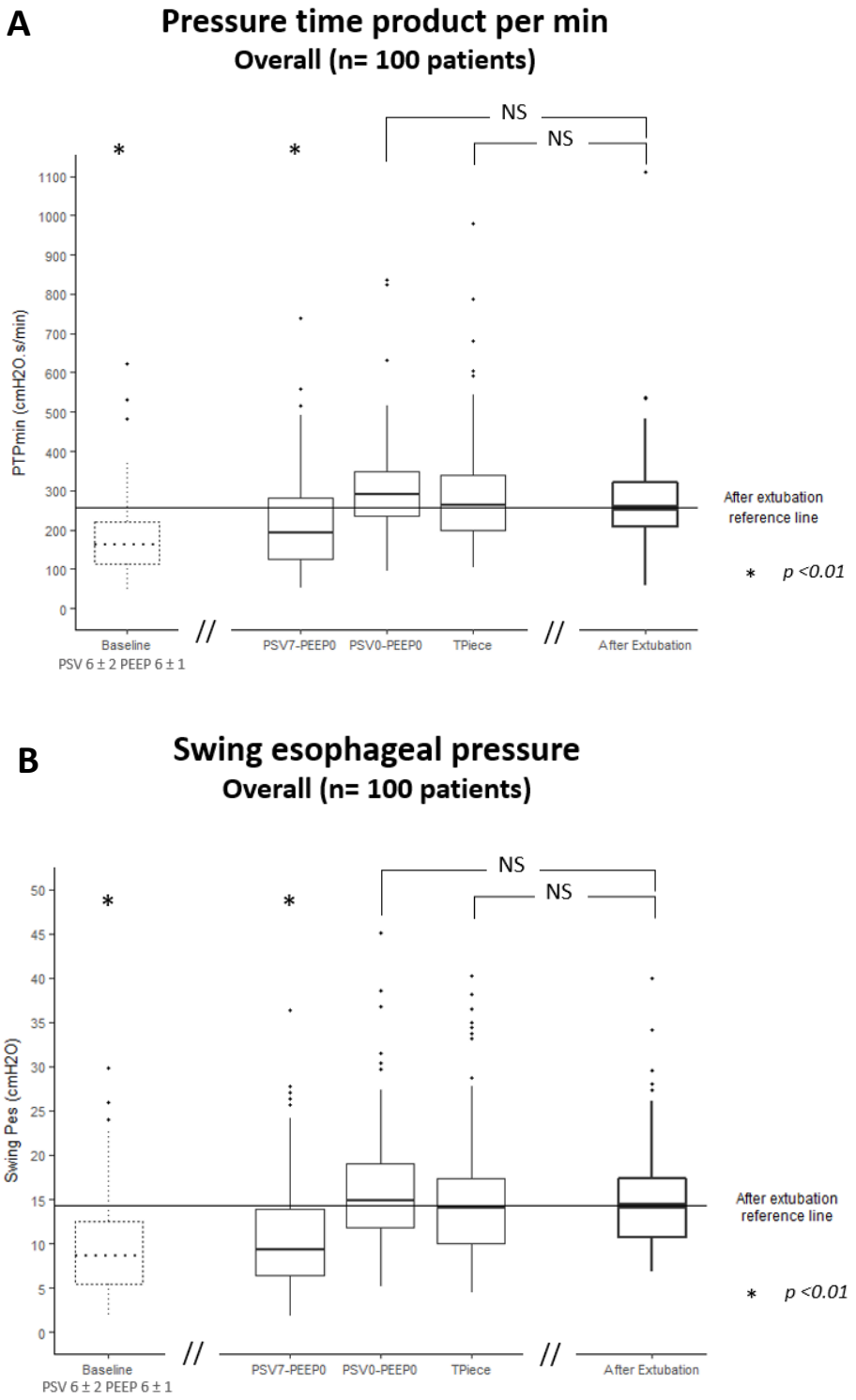


Figure S4: (A) Pressure time product per minute (PTPmin) and (B) esophageal pressure swing (Swing Pes) obtained at baseline, at the end of the three spontaneous breathing trials and 20 minutes after extubation for overall analyzed patients including outliers.

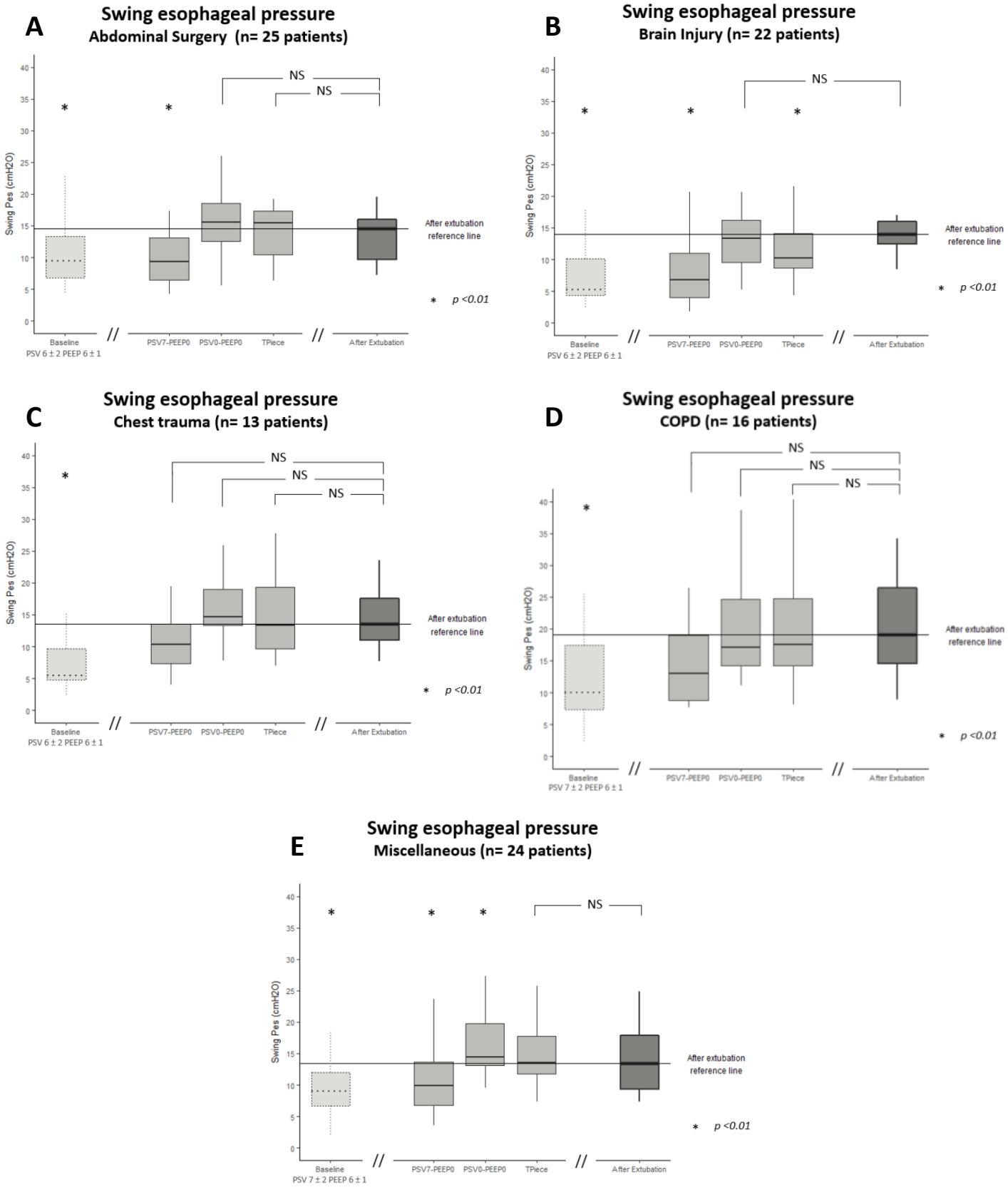


(A) Pressure time product (PTPmin) and (B) Esophageal swing pressure (Swing Pes) of overall patients (n=100 patients) obtained after 10 minutes of baseline ventilation, after 15 minutes of spontaneous breathing trial (SBT) with pressure support ventilation (PSV) of 7 cmH_2O without

positive end expiratory pressure (PEEP), after 15 minutes of SBT without PSV (0 cmH_2O) without PEEP, after 15 minutes of SBT with T-piece (only oxygenation without assistance) and 20 minutes after extubation. The scale has been modified to show all outliers.

NS=non-significant difference (p>0·01, Wilcoxon signed rank test)

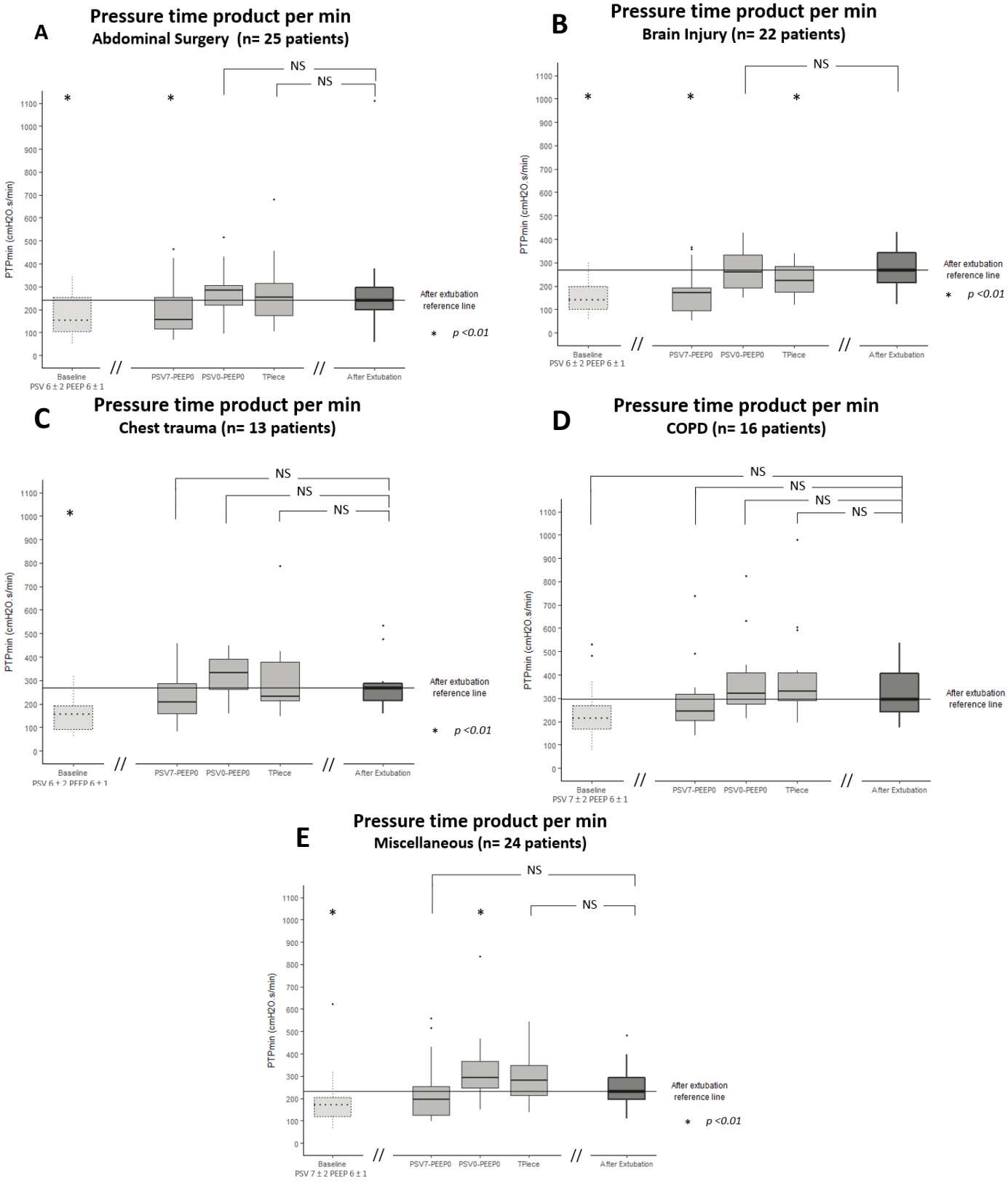
Figure S5: Esophageal pressure swing (Swing Pes) obtained at baseline, at the end of the three spontaneous breathing trials and 20 minutes after extubation according to the five phenotypes of patients: (A) post operative of abdominal surgery, (B) brain injury, (C) chest trauma, (D) chronic obstructive pulmonary disease (COPD) exacerbation and (E) miscellaneous patients.



Esophageal pressure swing (Swing Pes) of (A) post operative of abdominal surgery patients (n=25 patients), (B) patients with brain injury (n=22 patients), (C) patients with chest trauma (n=13 patients), (D) patients with chronic obstructive pulmonary disease (COPD) exacerbation (n=16 patients) and (E) miscellaneous patients (n=24 patients) obtained after 10 minutes of baseline ventilation, after 15 minutes of spontaneous breathing trial (SBT) with pressure support ventilation (PSV) of 7 cmH_2O without positive end expiratory pressure (PEEP), after 15 minutes of SBT without PSV (0 cmH_2O) without PEEP, after 15 minutes of SBT with T-piece (only oxygenation without assistance) and 20 minutes after extubation.

NS=non-significant difference (p>0·01, Wilcoxon signed rank test)

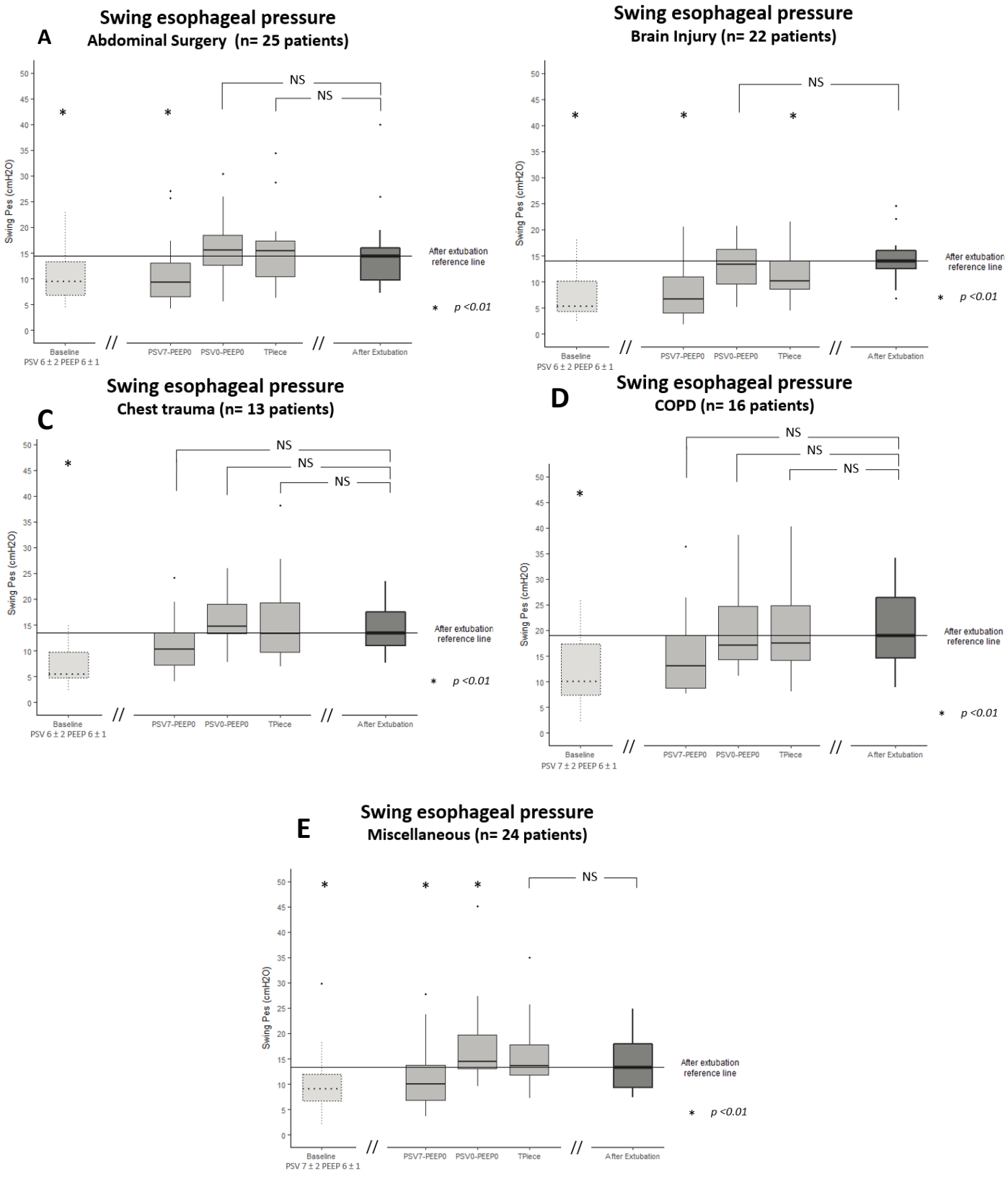
Figure S6: Pressure time product per minute (PTPmin) obtained at baseline, at the end of the three spontaneous breathing trials and 20 minutes after extubation according to the five phenotypes of patients including outliers: (A) post operative of abdominal surgery, (B) brain injury, (C) chest trauma, (D) chronic obstructive pulmonary disease (COPD) exacerbation and (E) miscellaneous patients.



Pressure time product (PTPmin) of (A) post operative of abdominal surgery patients (n=25 patients), (B) patients with brain injury (n=22 patients), (C) patients with chest trauma (n=13 patients), (D) patients with chronic obstructive pulmonary disease (COPD) exacerbation (n=16 patients) and (E) miscellaneous patients (n=24 patients) obtained after 10 minutes of baseline ventilation, after 15 minutes of spontaneous breathing trial (SBT) with pressure support ventilation (PSV) of 7 cmH_2O without positive end expiratory pressure (PEEP), after 15 minutes of SBT without PSV (0 cmH_2O) without PEEP, after 15 minutes of SBT with T-piece (only oxygenation without assistance) and 20 minutes after extubation. The scale has been modified to show all outliers.

NS=non-significant difference (p>0·01, Wilcoxon signed rank test)

Figure S7: Esophageal pressure swing (Swing Pes) obtained at baseline, at the end of the three spontaneous breathing trials and 20 minutes after extubation according to the five phenotypes of patients including outliers: (A) post operative of abdominal surgery, (B) brain injury, (C) chest trauma, (D) chronic obstructive pulmonary disease (COPD) exacerbation and (E) miscellaneous patients.



Esophageal pressure swing (Swing Pes) of (A) post operative of abdominal surgery patients (n=25 patients), (B) patients with brain injury (n=22 patients), (C) patients with chest trauma (n=13 patients), (D) patients with chronic obstructive pulmonary disease (COPD) exacerbation (n=16 patients) and (E) miscellaneous patients (n=24 patients) obtained after 10 minutes of baseline ventilation, after 15 minutes of spontaneous breathing trial (SBT) with pressure support ventilation (PSV) of 7 cmH_2O without positive end expiratory pressure (PEEP), after 15 minutes of SBT without PSV (0 cmH_2O) without PEEP, after 15 minutes of SBT with T-piece (only oxygenation without assistance) and 20 minutes after extubation. The scale has been modified to show all outliers.

NS=non-significant difference (p>0·01, Wilcoxon signed rank test)

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Résumé :

La dysfonction diaphragmatique est fréquente en réanimation et associée à l'échec du sevrage de la ventilation mécanique. La physiopathologie de l'atteinte diaphragmatique liée à l'excès d'assistance ventilatoire est bien décrite mais celle liée au manque d'assistance et à l'excès d'effort inspiratoire reste controversée. Au chevet du patient, l'évaluation de la fonction diaphragmatique est complexe et peut présenter quelques écueils. Au-delà du diaphragme, les pratiques dans l'évaluation de la capacité du patient à respirer sans assistance après extubation n'ont pas été réévaluées récemment avec les respirateurs de dernière génération.

Au cours de cette thèse nous avons mis en évidence l'impact de la sous assistance ventilatoire et de l'excès d'effort inspiratoire sur la fonction et la structure du diaphragme. Une nouvelle méthode simple d'évaluation de la fonction du diaphragme au chevet du patient a été développée et validée. Nous avons amélioré l'évaluation échographique avec l'ajout de l'élastographie dont l'interprétation a été soutenue par des données histologiques. Ce travail met aussi en avant de nouvelles pratiques d'épreuves de ventilation spontanées centrées sur le patient de réanimation et médecine périopératoire.

Abstract :

Diaphragmatic dysfunction is common in intensive care unit and associated with weaning failure. Ventilator induced diaphragm dysfunction due to over-assistance myotrauma (insufficient muscle loading) is well documented but the impact of under-assistance myotrauma (excess muscle loading) remains controversial and speculative. At bedside, the assessment of diaphragm function could be challenging and fraught with pitfalls. Beyond the diaphragm, practices for assessing patient's ability to sustain respiratory effort without assistance after extubation have not recently been updated, with the latest generation of ventilators.

In this thesis, we highlighted the impact of under-assistance and excessive inspiratory effort on diaphragm function and structure. A new simple approach to bedside assessment of diaphragm function has been developed and validated. We improved ultrasound assessment by adding elastography, which interpretation was supported by histological data. This thesis also highlights new practices for patient-centered spontaneous breathing trials in intensive care and perioperative medicine.

Résumé :

La dysfonction diaphragmatique est fréquente en réanimation et associée à l'échec du sevrage de la ventilation mécanique. La physiopathologie de l'atteinte diaphragmatique liée à l'excès d'assistance ventilatoire est bien décrite mais celle liée au manque d'assistance et à l'excès d'effort inspiratoire reste controversée. Au chevet du patient, l'évaluation de la fonction diaphragmatique est complexe et peut présenter quelques écueils. Au-delà du diaphragme, les pratiques dans l'évaluation de la capacité du patient à respirer sans assistance après extubation n'ont pas été réévaluées récemment avec les respirateurs de dernière génération.

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