Evaluation et impact de la dysfonction diaphragmatique au cours du sevrage de la ventilation mécanique chez le patient adulte de réanimation

Martin Dres

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Dr Martin DRES

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- M. Alain COMBES : Président
- M. Armand MEKONTSO DESSAP : Rapporteur
- M. Alain MERCAT : Rapporteur
- Mme Nadia AISSAOUI : Examinateur
- M. Thomas SIMILOWSKI : Examinateur
- M. Alexandre DEMOULE : Directeur de Thèse

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Préambule et introduction

La ventilation permet la réalisation des échanges gazeux indispensables à la vie. Chez les mammifères, cette fonction est permise par la mobilisation de l'air à travers les voies aériennes jusqu'au alvéoles. Cette mobilisation est déterminée par la production de pressions motrices générées par les muscles respiratoires dont le diaphragme, principal muscle inspiratoire. Au cours des formes les plus sévères de l'insuffisance respiratoire aiguë, la survie des patients repose sur la mise en place de la ventilation mécanique, technique de réanimation délivrée par un ventilateur qui vise à assister partiellement voire totalement la ventilation. Bien qu'il s'agisse d'un traitement permettant de sauver la vie, le recours à la ventilation mécanique peut s'associer à la survenue de complications à même de modifier significativement le pronostic lié à la maladie initiale. Dès lors, l'exigence des équipes médicales et soignantes se porte sur la nécessité de séparer en toute sécurité et le plus tôt possible les patients du ventilateur. Cette démarche est appelée sevrage de la ventilation mécanique. Elle fait l'objet de nombreux travaux de recherche qui ont abouti à une prise en charge de plus en plus standardisée. Pour une proportion faible de patients mais représentant une importante consommation de soins et de journées d'hospitalisation, le sevrage est difficile. Le développement au cours du séjour en réanimation d'une réduction de la force musculaire globale, dans le cadre d'une entité nosologique intitulée neuromyopathie de réanimation, est un facteur de risque reconnu d'échec du sevrage de la ventilation mécanique. En tant que principal muscle inspiratoire assurant la ventilation, le diaphragme est également susceptible d'être affecté par une diminution de sa contractilité. Le rôle de la dysfonction diaphragmatique dans l'échec du sevrage de la ventilation mécanique est suggéré par la littérature. Toutefois, ce rôle n'est pas établi formellement car

les techniques d'investigations de référence de la fonction diaphragmatique sont difficilement réalisables en réanimation. En effet, la méthode de référence repose sur la mesure de la pression intra-thoracique générée par le diaphragme en réponse à une stimulation des nerfs phréniques. Cette méthode requiert une expertise et un matériel limitant son utilisation hors du périmètre des centres experts. Pour cette raison, le développement d'outils permettant d'identifier et de suivre une telle dysfonction est une problématique majeure en réanimation.

Dans sa première partie, cette thèse se propose de discuter de l'état actuel des connaissances sur la dysfonction diaphragmatique au cours du sevrage de la ventilation mécanique et de son association avec la neuromyopathie de réanimation. Dans cet objectif, nous détaillerons d'abord les caractéristiques anatomiques du diaphragme avant de décrire sa fonction normale et les principales méthodes d'investigation de cette fonction. Nous discuterons ensuite du rôle du diaphragme au cours du sevrage de la ventilation mécanique qui représente une condition d'observation unique de son fonctionnement.

La seconde partie de cette thèse est organisée autour de trois articles publiés et d'un manuscrit en cours de relecture. A partir de ces travaux nous décrirons l'impact de la dysfonction diaphragmatique sur la réussite du sevrage et sa coexistence avec la neuromyopathie de réanimation (chapitre 1). Nous évaluerons comment la fonction du diaphragme peut être étudiée au lit du patient en mesurant l'épaississement du diaphragme comme reflet de sa fonction (chapitre 2) et le couplage neuro-mécanique comme indicateur de son activité (chapitre 3). Enfin, nous examinerons la possibilité de prédire l'issue du sevrage à partir de la mesure de la fonction diaphragmatique (chapitre 4). Une revue générale traitant de la dysfonction diaphragmatique chez les patients de réanimation complète les quatre travaux susmentionnés.

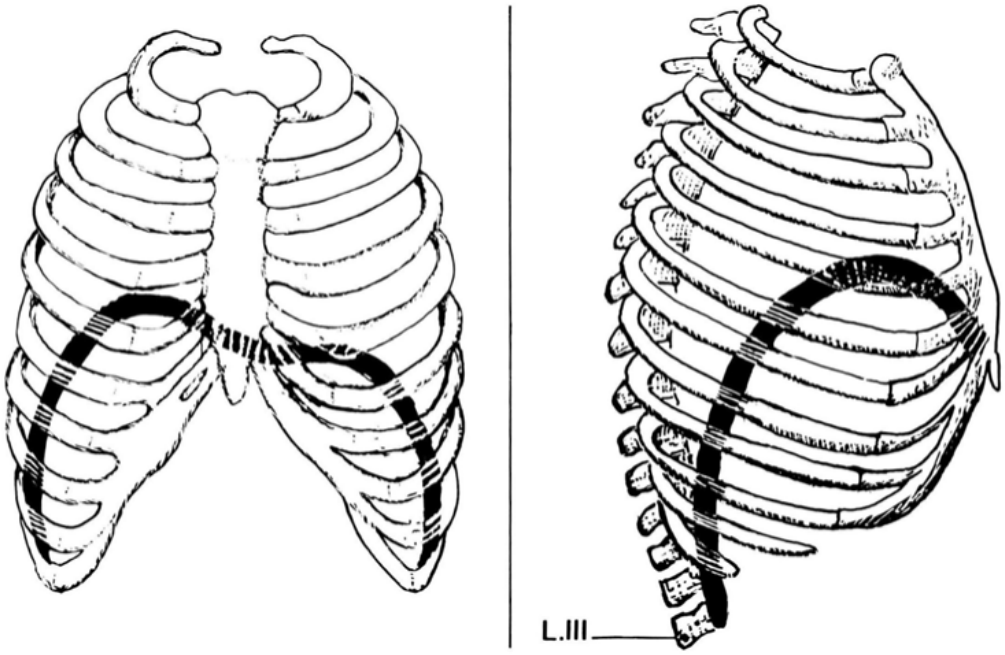
Synthèse des connaissances

1. Anatomie, physiologie et fonction du diaphragme humain adulte

1.1 Anatomie

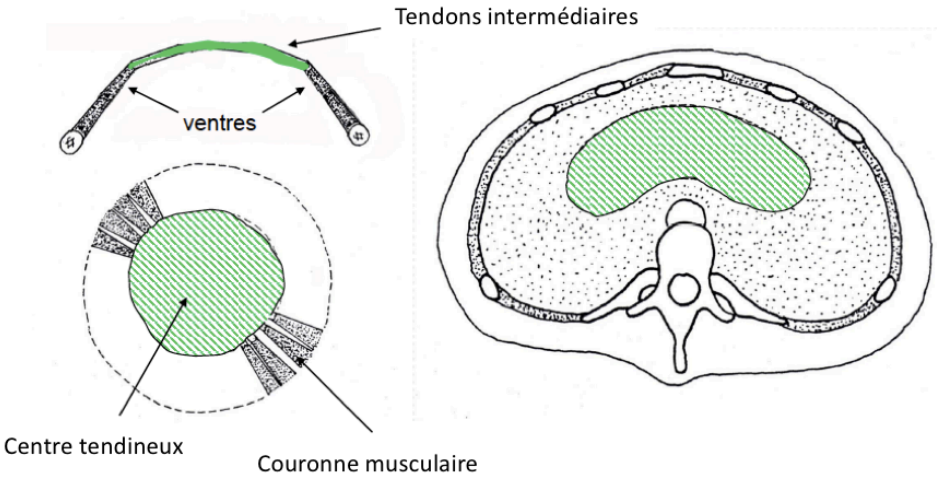
Le diaphragme est le principal muscle inspiratoire et le seul à assurer la ventilation 24 heures sur 24. Le diaphragme est une cloison musculo-tendineuse qui sépare la partie inférieure du thorax de la partie supérieure de l'abdomen. Il peut être grossièrement décrit comme un dôme ou une coupole descendant plus bas en arrière qu'en avant (**Figure 1**).

Figure 1. Représentation schématique de la coupole diaphragmatique, d'après (1).



Le diaphragme comporte une structure tendineuse centrale d'où rayonnent des fibres musculaires qui s'insèrent à la périphérie avec une orientation à dominante verticale sur les structures squelettiques (**Figure 2**).

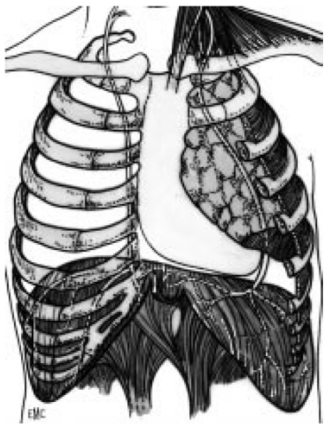
Figure 2. Représentation de la structure tendineuse du diaphragme (Illustration de Philippe Chaffanjon, Université Joseph Fourier de Grenoble)



A l'arrière, les fibres crurales s'insèrent sur la face antérolatérale des vertèbres lombaires et sur l'arcade du muscle psoas. A l'avant, les fibres musculaires s'attachent sur la partie postérieure de l'appendice xiphoïde. A gauche et à droite, les fibres diaphragmatiques descendent sur les faces internes des six cartilages costaux inférieurs et sur la partie adjacente des côtes correspondantes, définissant une zone d'intérêt pour l'échographie : la zone d'apposition, dont la hauteur représente schématiquement le tiers de la hauteur totale du gril costal. La structure tendineuse centrale qui se situe à la partie inférieure du médiastin laisse passer les structures digestives, nerveuses et vasculaires par l'intermédiaire du hiatus aortique, œsophagien et cave inférieur.

Le diaphragme est innervé par les nerfs phréniques gauche et droit, issus du plexus cervical C4. Les deux nerfs phréniques descendent de part et d'autre du médiastin pour finir en une terminaison rayonnée sur chacune des coupoles diaphragmatiques (**Figure 3**).

Figure 3. Innervation du diaphragme (2)



Issus du plexus cervical, les deux nerfs phréniques sont caractérisés par une innervation motrice exclusive du diaphragme. Ils sont accessibles à des techniques de stimulation permettant une contraction du diaphragme non volitionnelle et indépendante de celle des autres muscles respiratoires. La vascularisation du diaphragme est réalisée par six artères atteignant de chaque côté les faces supérieure et inférieure de chaque hémidiaphragme. Sur la face supérieure, l'artère diaphragmatique supérieure, collatérale de la mammaire interne, accompagne le nerf phrénique. La vascularisation de la face supérieure est également réalisée par l'artère musculo-phrénique, branche terminale de la mammaire interne. A la face inférieure, la vascularisation est réalisée par l'artère diaphragmatique inférieure, issue de l'aorte abdominale. L'anastomose est réalisée par des branches venant des artères phréniques, des mammaires internes et intercostales (3). La microcirculation très riche permet un apport métabolique important et rapide grâce au recrutement capillaire.

Le diaphragme est un muscle strié squelettique. Chez le sujet sain, il est constitué pour un peu plus de la moitié de fibres musculaires lentes de type 1, caractérisées par une grande résistance à la fatigue car fonctionnant en aérobie (4). L'autre moitié est représentée équitablement par des fibres rapides de type 2A, fonctionnant en aérobie et relativement

résistantes à la fatigue et des fibres rapides de type 2B, fonctionnant en anaérobie et rapidement fatigables (5). Les fibres musculaires diaphragmatiques sont proportionnellement plus riches en myoglobine et en systèmes protecteurs anti-oxydants que les autres muscles squelettiques (4). Ce profil original fait du diaphragme un muscle très résistant à la fatigue et aux agressions oxydantes.

1.2 Physiologie

L'action principale du diaphragme sur la cage thoracique peut être schématiquement représentée par le fonctionnement d'un piston dans une seringue. La contraction du muscle entraîne son raccourcissement essentiellement au niveau de la zone d'apposition. La contraction entraîne un aplatissement de sa structure générant le volume courant par une diminution de la pression intra-thoracique (6). L'air admis dans les voies aériennes supérieures est alors mobilisé jusqu'aux alvéoles où a lieu les échanges gazeux permettant l'oxygénation du sang et l'élimination du gaz carbonique.

1.3 Déterminants de la fonction diaphragmatique

En tant que muscle, le diaphragme a de multiples fonctions. Il participe au maintien de la posture, à la ventilation, à la toux, à la défécation, à l'accouchement et à l'homéostasie. Le développement d'une force et la capacité à se raccourcir sont deux fonctions caractéristiques du diaphragme. La force est généralement estimée par la pression produite par la contraction et le raccourcissement ainsi produit par l'analyse des variations de volumes pulmonaires ou du déplacement des structures de la cage thoracique. Comme cela sera détaillé ci-dessous, les facteurs influençant la fonction du diaphragme sont multiples. Ils interviennent à tous les niveaux de la chaîne effectrice : la commande centrale, la conduction nerveuse jusqu'à la transmission neuromusculaire, les propriétés contractiles du

muscle et les rapports du muscle avec la cage thoracique et le compartiment abdominal (mécanique respiratoire). A chaque étape de cette segmentation, plusieurs affections sont susceptibles d'induire une dysfonction diaphragmatique (**Tableau 1**).

Tableau 1. Liste non exhaustive des affections susceptibles d'induire une dysfonction diaphragmatique

Chaîne de la commande		Affections
Commande centrale	Cortex	Accident vasculaire cérébral Sclérose en plaque
	Tronc cérébral	Syndrome d'Ondine Accident vasculaire cérébral
	Moelle épinière	Lésion médullaire (traumatisme, ischémie)
Transmission	Motoneurone	SLA SEP Traumatisme
	Nerfs	Syndrome de Guillain Barré
	Plaque neuromusculaire	Myasthénie
Muscle	Myopathies congénitales	Maladie de Duchenne Myopathie de Steinert
	Myopathies acquises	Inactivité prolongée (ventilation mécanique)
Système respiratoire	Voies aériennes	BPCO
	Parenchyme	Emphysème
	Cage thoracique	Cyphoscoliose
	Abdomen	Eventration

BPCO : Bronchopneumopathie chronique obstructive ; SLA : Sclérose latérale amyotrophique ; SEP : Sclérose en plaque

La commande de la ventilation est double : automatique, localisée au niveau du tronc cérébral ; et volontaire, localisée au niveau du cortex. La commande automatique assure la ventilation dans son adaptation homéostatique (exercice, sommeil, perturbations métaboliques) de la naissance à la mort, vingt-quatre heures sur vingt-quatre. La commande volontaire permet la réalisation de manœuvres complexes (suspension de la ventilation,

effort maximal) qui autorisent notamment la réalisation d'actions respiratoires (apnée, épreuves fonctionnelles respiratoires) et extra-respiratoires comme la défécation, la posture ou l'accouchement. Lors de ces actions, la commande volontaire inhibe la commande automatique, mais de façon temporaire seulement. Le rôle de la commande centrale dans la genèse de la contraction diaphragmatique doit être pris en compte lorsque l'on envisage une exploration de la fonction du diaphragme chez les patients de réanimation chez lesquels la commande centrale peut être diminuée du fait de l'utilisation de médicaments sédatifs ou en raison d'une maladie sous-jacente (accident vasculaire cérébral, coma). Elle peut être au contraire augmentée chez des patients présentant une insuffisance respiratoire aiguë. Au niveau des motoneurones et de la jonction neuromusculaire, la transmission de la commande peut être perturbée par des maladies (sclérose latérale amyotrophique, syndrome de Guillain-Barré, myasthénie) ou par l'utilisation de médicaments inhibant la transmission du signal spécifiquement au niveau de la plaque neuromusculaire (curares).

La relation entre pression et force est complexe et il est important de prendre en compte la géométrie de la cage thoracique dans la conversion de la force en pression. Elle est donc déterminée par la configuration géométrique du diaphragme avant contraction. La configuration géométrique du diaphragme est déterminée par ses rapports anatomiques notamment avec le squelette par l'intermédiaire des tendons, par le volume pulmonaire et par la pression intra-abdominale. Ceci explique que toute modification de l'anatomie ou des caractéristiques mécaniques de la paroi thoracique peut altérer la fonction du diaphragme, indépendamment de ses propriétés contractiles intrinsèques. A titre d'exemple, on peut citer le cas des patients porteurs de bronchopneumopathie chronique obstructive (BPCO) qui sont caractérisés aux stades avancés de la maladie par une distension thoracique. Cette distension peut être responsable d'une augmentation du diamètre de la cage thoracique. La

conséquence est un aplatissement du diaphragme ce qui induit un chevauchement non optimal des ponts actine-myosine et une diminution de sa capacité à produire une force (7). Une autre configuration liée aux caractéristiques du compartiment abdominal peut gêner le rendement de la contraction diaphragmatique. Si le compartiment abdominal ne s'oppose que faiblement à la descente du diaphragme au cours de l'inspiration, par exemple du fait d'une éventration, l'abaissement des coupoles diaphragmatiques est plus marqué et la pression générée par l'expansion thoracique est donc plus faible.

2. Techniques d'investigations de la fonction du diaphragme

L'absence d'accessibilité anatomique du diaphragme impose le recours à des moyens indirects d'explorations. La première approche consiste à enregistrer des signaux non spécifiques d'une contraction isolée du diaphragme (pressions, volumes, activité électromyographique). Lors de cette approche, les signaux mesurés sont produits par une contraction globale des muscles respiratoires en ventilation spontanée ou lors de manœuvres statiques ou dynamiques. Le diaphragme participe naturellement à la production de ces signaux mais sa contribution respective ne peut être quantifiée. L'autre approche a pour objectif de provoquer artificiellement une contraction isolée du diaphragme et d'étudier l'ensemble des signaux produits en réponse à cette stimulation (8).

2.1 Signaux non spécifiques du diaphragme

Les principaux signaux non spécifiques sont la pression statique à la bouche, la pression dynamique à l'ouverture des voies aériennes, la pression d'occlusion, la pression œsophagienne et ses dérivés, l'électromyographie de surface et les volumes pulmonaires notamment la capacité vitale.

2.1.1 Pression statique à la bouche

Cette première approche intègre la fonction de l'ensemble des muscles respiratoires. Elle est réalisée de manière simple et non invasive en mesurant la pression à la bouche soutenue pendant une seconde au cours d'un effort inspiratoire statique maximal : pression inspiratoire maximale (9). Cette manœuvre demande la pleine collaboration du sujet, ce qui n'est pas toujours possible, notamment en réanimation. Dans le cas particulier des patients ventilés artificiellement, il est possible d'obtenir une information équivalente en mesurant la pression dans les voies aériennes lors d'efforts inspiratoires contre une occlusion d'une

seconde même si la reproductibilité de cette méthode est discutable (10). La pression inspiratoire maximale peut aussi être mesurée en utilisant une valve unidirectionnelle qui permet l'expiration tout en interdisant l'inspiration. Cette approche permet de réaliser l'effort inspiratoire maximal à un volume pulmonaire approchant le volume résiduel, volume auquel la pression inspiratoire maximale est supposée maximale (11). L'autre intérêt de cette méthode dite « de Marini » est de permettre la mesure de la pression inspiratoire maximale chez les sujets non coopérants. L'approche de Marini doit être préférée à la méthode d'occlusion car elle produit des pressions inspiratoires maximales plus élevées (12). L'interprétation des résultats en réanimation est rendue difficile par la grande variabilité interindividuelle de la force inspiratoire et par l'absence de normes.

2.1.2 Pression dynamique (Sniff-test)

Etant donné qu'une manœuvre de reniflement est plus naturelle que l'effort inspiratoire maximal contre une occlusion, la mesure de la pression nasale au travers d'un tampon occluant une narine durant une manœuvre de reniflement accomplie à la capacité résiduelle fonctionnelle par l'autre narine (Snif Nasal Inspiratory Pressure : SNIP ou Sniff-test) est une alternative intéressante à la pression inspiratoire maximale (8). La pression obtenue est un test dynamique, pendant lequel la pression nasale reflète la pression œsophagienne (13). Le Sniff test semble plus facile à réaliser pour les sujets car la coordination requise est plus naturelle qu'au cours d'une manœuvre statique (14). Toutefois, là aussi il est nécessaire d'obtenir une étroite collaboration entre le technicien et le patient.

2.1.3 Pression d'occlusion

Cette grandeur est mesurée au terme des 100 premières millisecondes d'une inspiration contre occlusion. Il s'agit d'un indice ($P_{0,1}$) témoignant de l'intensité de la commande centrale (15). Toutefois, d'autres déterminants interviennent dans la production de cette grandeur, notamment la fonction des muscles inspiratoires et les voies de conduction nerveuses périphériques. Une élévation de la $P_{0,1}$ témoigne constamment d'une forte intensité de la commande centrale. En revanche, des valeurs basses de $P_{0,1}$ peuvent être la conséquence d'une anomalie de la force musculaire respiratoire, des voies de conduction ou d'une diminution de la commande centrale. Il s'agit donc d'un indice composite de la commande neuromusculaire. Il est à noter que la $P_{0,1}$ peut être sous-estimée par la présence d'une pression télé-expiratoire intrinsèque positive, cette dernière imposant un effort inspiratoire pouvant être important mais non pris en compte lors de la mesure (16). La mesure de la $P_{0,1}$ nécessite une valve unidirectionnelle et un capteur de pression. Chez les patients de réanimation, la $P_{0,1}$ peut être obtenue directement sur le ventilateur mais la précision de la mesure dépend vraisemblablement du type de machine.

2.1.4 Produit pression-temps et travail respiratoire

La fonction du diaphragme et des autres muscles respiratoires peut être mesurée en quantifiant les variations de pression pleurale que leur contraction induit et en connaissant les propriétés passives de la paroi thoracique (17). En pratique la pression pleurale est estimée par la pression œsophagienne (17). A partir de la relation donnée par pression œsophagienne au cours du temps, il est possible d'intégrer le travail respiratoire (work of breathing, WOB) et le produit pression-temps (PTP). L'obtention du PTP et du WOB impose de connaître la compliance de la paroi thoracique qui est habituellement estimée à 4% de la capacité vitale par cmH_2O (18). L'autre possibilité, plus rigoureuse, consiste à mesurer la

relation pression-volume de la paroi thoracique au cours d'une inspiration passive, le sujet étant endormi et anesthésié. Toutefois, le calcul du WOB a plusieurs limites — notamment en réanimation — ce qui conduit à lui préférer le PTP (17). Le PTP représente l'intégrale du signal de pression œsophagienne (comme reflet de la pression pleurale) en fonction du temps. En réanimation, il s'agit d'un indice très utile pour quantifier l'effort des muscles inspiratoires car il peut être partitionné en plusieurs composantes : PTP nécessaire à vaincre la pression télé-expiratoire positive intrinsèque, PTP réalisé pour déclencher le ventilateur. La mesure du PTP est très utilisée en recherche mais reste relativement confidentielle en pratique clinique (17).

2.1.5 Electromyographie de surface

L'activité électrique diaphragmatique peut être enregistrée par l'intermédiaire d'électrodes de surface collées sur la peau au niveau de la zone d'apposition du diaphragme sur la face interne des côtes inférieures. En pratique, cet enregistrement est peu utilisé car il résulte de la sommation des activités électriques des muscles et groupes musculaires placés entre les électrodes et le diaphragme. Il n'est donc pas spécifique du diaphragme. En revanche, il est utilisé pour s'assurer du bon positionnement d'électrodes destinées à recueillir une réponse à la stimulation phrénique.

2.1.6 Mesures des volumes

L'atteinte des muscles respiratoires peut être évaluée indirectement par la mesure de la capacité vitale. Chez un sujet dont la cage thoracique et le parenchyme pulmonaire sont normaux, une pression transpulmonaire de l'ordre de 30 à 40 cmH_2O est suffisante pour atteindre la capacité pulmonaire totale. La chute de la capacité vitale s'accélère à un stade avancé de l'atteinte musculaire du fait de sa relation curvilinéaire avec la force des

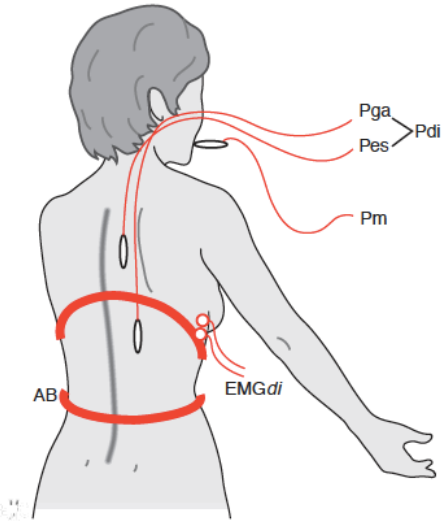
muscles inspiratoires. La mesure de la capacité vitale est simple, non coûteuse, non invasive, facilement disponible. L'expérience acquise dans le cadre des maladies neuromusculaires (syndrome de Guillain Barré, myasthénie) a montré l'intérêt pour cette grandeur en tant que marqueur évolutif de l'atteinte musculaire respiratoire (19, 20).

2.2 Signaux spécifiques du diaphragme

2.2.1 Pression transdiaphragmatique

L'étude spécifique de la fonction diaphragmatique, c'est à dire isolément de la participation des autres muscles inspiratoires, peut se faire par la mesure de la pression transdiaphragmatique. La pression transdiaphragmatique est définie par la différence entre la pression régnant dans la cavité thoracique et la pression de la cavité abdominale (21). La pression intra-thoracique n'étant pas accessible dans la pratique clinique, c'est la pression œsophagienne qui est mesurée en lieu et place (17), la pression abdominale étant mesurée dans l'estomac (17). L'obtention de ces pressions nécessite l'insertion de cathéters munis de ballonnets positionnées respectivement dans l'œsophage et dans l'estomac (21) (**Figure 4**).

Figure 4. Exploration de la fonction diaphragmatique par la mesure de la pression transdiaphragmatique (Pdi) à partir de la pression œsophagienne (Pes) et gastrique (Pga). La mesure de Pes et Pga se fait par l'intermédiaire de sondes à ballonnets (2).



La pression transdiaphragmatique est égale à la différence entre la pression œsophagienne et la pression gastrique. La mesure des contributions respectives de la pression abdominale et de la pression thoracique à la pression transdiaphragmatique lors de la ventilation spontanée peut donner des indications sur le fonctionnement du diaphragme (indice de Gilbert) (22). Le diaphragme, lors de sa contraction abaisse la pression œsophagienne et simultanément augmente la pression gastrique, la différence entre ces deux pressions, la pression transdiaphragmatique est non nulle. Inversement, en cas de dysfonction diaphragmatique, la contraction isolée des muscles inspiratoires extra-diaphragmatiques abaisse la pression œsophagienne mais négative également la pression gastrique, la pression transdiaphragmatique est nulle.

2.2.2 Electromyographie du diaphragme

Le recueil de l'activité électrique du diaphragme est ancien (23). Le signal d'électromyographie (EMG) du diaphragme peut être recueilli par des aiguilles

intramusculaires et par voie œsophagienne (diaphragme crural). L'utilisation d'aiguilles pour obtenir le signal EMG rend difficilement envisageable la généralisation de cette technique du fait d'un risque faible mais existant de pneumothorax et de plaies hépatiques et spléniques. En revanche, la détection de l'activité EMG du diaphragme crural par électrodes œsophagiennes a récemment progressé avec la possibilité de recueillir de façon continue l'activité électrique du diaphragme (EAdi). L'analyse du signal nécessite de mettre en place des filtres, notamment pour le bruit de fond, d'au moins 20 Hz puisque le signal électrique du diaphragme a une fréquence minimale de 20Hz. Le traitement du signal permet d'obtenir une onde d'activité électrique diaphragmatique qui suit le tracé de pression dans les voies aériennes de manière synchrone et proportionnelle (24). L'EAdi peut être aisément décrit des manières suivantes : pic de l'EAdi (EAdimax), aire sous la courbe du temps inspiratoire de l'EAdi (EAdiAUC), différence entre l'EAdi maximal et l'EAdi minimal (EAdi). L'utilisation de l'EAdi a permis l'exploration d'un signal relativement spécifique du diaphragme qui permet d'estimer l'effort inspiratoire (25), de titrer le niveau d'assistance ventilatoire (26) ou encore d'évaluer l'interaction patient-ventilateur (27, 28).

2.2.3 Détection des signaux spécifiques du diaphragme par la technique de stimulation des nerfs phréniques

La stimulation des nerfs phréniques permet l'exploration spécifique de la fonction du diaphragme et de la conduction phrénique indépendamment de la coopération du patient. Cette technique consiste à provoquer artificiellement une contraction isolée du diaphragme par stimulation des nerfs phréniques et à mesurer en réponse à cette stimulation des signaux physiologiques : pressions, conduction des potentiels d'action. A ce titre, la pression buccale et la pression œsophagienne deviennent spécifiques de la fonction diaphragmatique lors de la stimulation des nerfs phréniques. La stimulation phrénique permet d'apprécier la

capacité du diaphragme à produire une pression inspiratoire, d'évaluer la conduction phrénique et de détecter l'existence d'un bloc de conduction neuromusculaire. La stimulation phrénique peut être réalisée au moyen d'un stimulus électrique ou magnétique (29). La stimulation électrique des nerfs phréniques est la technique de référence de l'exploration diaphragmatique car elle induit une stimulation isolée du diaphragme à la condition de ne stimuler que le nerf phrénique sans stimuler le plexus brachial adjacent. Ceci nécessite un repérage minutieux des structures anatomiques afin de s'assurer d'un recrutement optimal des fibres nerveuses du nerf phrénique à l'exclusion de tout autre pour éviter les erreurs d'interprétation. L'inconvénient principal de cette technique réside dans le repérage du nerf phrénique qui peut être parfois difficile notamment du fait des variations anatomiques. Par ailleurs, la répétition des stimulations électriques est douloureuse. Enfin, la nécessité de stimuler les deux nerfs phréniques simultanément et la présence de dispositifs comme un collier de trachéotomie ou un cathéter jugulaire rendent compliquée l'utilisation de la technique en réanimation.

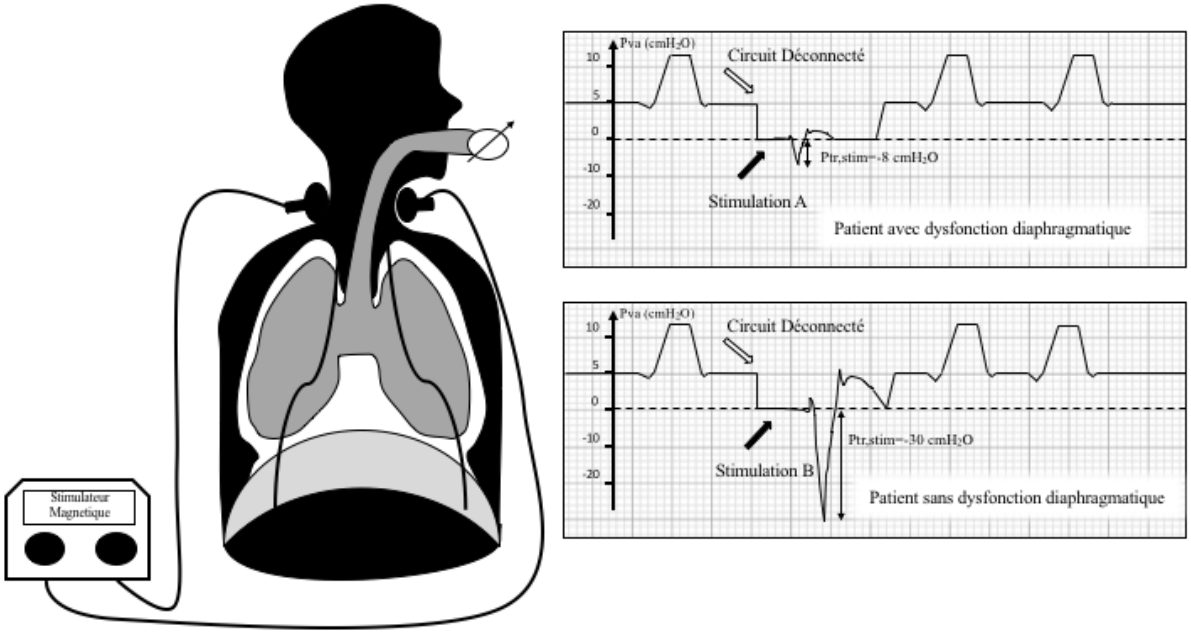
La stimulation magnétique est largement plus accessible dans ce contexte (30, 31). Cette technique a été développée pour pallier les inconvénients de la stimulation électrique (30). Elle repose sur le principe qu'un champ magnétique pulsé produit par la décharge d'un courant de forte intensité dans une bobine de fil métallique traverse les barrières osseuses et cutanée en étant très peu atténué. Elle peut être effectuée par voie cervicale postérieure ou antérieure (29). Au même titre que la stimulation électrique, les pressions habituellement mesurées (œsophagienne, gastrique, trachéale) ont l'intérêt d'être indépendantes de la volonté du patient et donc reproductibles. En revanche, les principales limites de cette technique sont la lourdeur de l'équipement nécessaire et l'expertise qui toutes deux restreignent sa généralisation.

L'utilisation de la technique de stimulation des nerfs phréniques en réanimation est rendue plus simple dans sa réalisation lorsque le signal de pression est mesuré au niveau des voies aériennes supérieures (pression trachéale), à l'extrémité de la sonde d'intubation ou de la canule de trachéotomie plutôt que lorsqu'il repose sur la mesure de la pression transdiaphragmatique qui nécessite la mise en place de ballonnets gastrique et œsophagien. En réalité, la corrélation entre la pression transdiaphragmatique et la pression trachéale n'est pas excellente (32, 33). Ce n'est en réalité pas un problème car ce qui importe surtout, c'est de mesurer la transformation de la contraction diaphragmatique en dépression pleurale (c'est à dire œsophagienne) plutôt que d'évaluer la fonction propre du diaphragme comme le ferait la pression transdiaphragmatique. Et justement, la corrélation entre la pression trachéale et la pression œsophagienne est satisfaisante (32). A partir des données existantes chez le sujet sain et de quelques séries réalisées chez des patients à l'occasion de chirurgie programmée (34, 35), il est estimé qu'une valeur de pression trachéale en réponse à une stimulation (Ptr,stim) < 11 cmH_2O est en faveur d'une dysfonction diaphragmatique (**Figure 5).** A noter que des précautions dans l'interprétation des valeurs basses de Ptr,stim doivent être prises en cas de distension thoracique génératrice de pression télé-expiratoire positive intrinsèque susceptible de minorer la pression générée par la contraction du diaphragme.

Electrique ou magnétique, un critère de qualité commun aux deux techniques repose sur l'assurance que la stimulation concerne la totalité des fibres nerveuses du nerf phrénique et qu'elles soient dépolarisées totalement. Dans cet objectif, il faut réaliser une stimulation « supramaximale » pour garantir un recrutement de la totalité des fibres nerveuses. Ceci peut être fait en utilisant une intensité de stimulation supérieure d'au moins 10% à l'intensité provoquant une réponse électromyographique d'amplitude maximale. Pour

obtenir une stimulation supramaximale, une courbe de recrutement décrivant l'évolution de l'amplitude de la réponse électromyographique en fonction de l'intensité de la stimulation est construite. In fine, si le recrutement est supramaximal et le nerf phrénique parfaitement repéré, la stimulation induit une contraction diaphragmatique reproductible et une information spécifique des propriétés contractiles du muscle.

Figure 5. Evaluation de la fonction diaphragmatique par la technique de stimulation magnétique des nerfs phréniques (d'après Dres et coll. (36))



Représentation schématique de la technique de stimulation magnétique des nerfs phréniques chez un patient placé sous ventilation mécanique (Aide Inspiratoire). Deux bobines magnétiques sont positionnées au niveau de la portion initiale des deux nerfs phréniques. La pression dans les voies aériennes (Pva) est enregistrée à l'extrémité proximale de la sonde d'intubation. Dans un premier temps, le circuit est déconnecté (flèche blanche) et la stimulation est produite par le stimulateur magnétique (flèche noire). La fonction diaphragmatique est mesurée comme étant sa capacité à générer une dépression intrathoracique en réponse à la stimulation phrénique. La stimulation A est suivie par une capacité réduite à générer une pression (- 8 cmH_2O) alors que la stimulation B est suivie par une capacité normale à générer une pression (- 30 cmH_2O).

Les indications d'exploration de la fonction diaphragmatique en réanimation sont dominées par les situations de sevrage complexes de la ventilation qui voient se poser la question de l'imputabilité d'une atteinte des nerfs phréniques ou du diaphragme (ou des deux). Devenu exceptionnel de nos jours, le risque de lésion phrénique dans les suites d'une intervention de chirurgie cardiaque était une indication courante à l'exploration de la fonction diaphragmatique. Enfin, certains tableaux neurologiques complexes associant des troubles centraux et périphériques peuvent bénéficier d'une exploration de la fonction diaphragmatique pour identifier les composantes centrale ou périphérique, nerveuse ou musculaire d'une dépendance à la ventilation mécanique.

2.3 Evaluation échographique de la fonction diaphragmatique

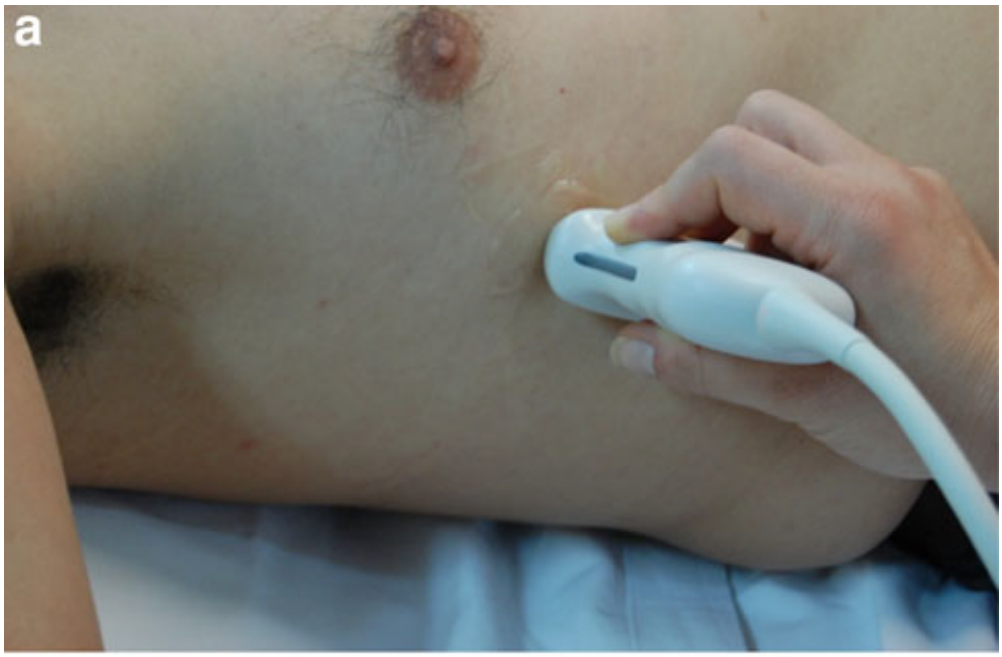
La zone d'apposition du diaphragme contre la paroi thoracique offre une fenêtre d'observation ultrasonore de l'épaisseur et de l'épaississement du muscle. L'échographie est une technique d'évaluation simple, reproductible et non invasive de la fonction du diaphragme. Décrite en 1989 (37), cette méthode a été évaluée chez les sujets sains (37, 38), les patients atteints de BPCO (39), les patients porteurs d'une maladie neuromusculaire (38, 40, 41) et chez des patients de réanimation (42–49). Deux approches sont décrites : l'approche intercostale et l'approche sous costale. Bien que théoriquement le diaphragme puisse être visualisé bilatéralement, l'approche gauche est plus difficile d'accès que l'approche droite. Cette asymétrie en faveur de l'hémidiaphragme droit est la conséquence d'une présentation plus superficielle de l'hémidiaphragme droit liée au volume du foie plus important que celui de la rate à gauche. De fait, la plupart des travaux publiés rapportent des données concernant l'hémidiaphragme diaphragme droit. Pour les deux approches, l'observation du diaphragme est réalisée avec 1) le mode bidimensionnel (''B-mode''), dans lequel le diaphragme est représenté dans le plan axial en temps réel, et 2) le mode temps-

mouvement (‘’M-mode’’) qui permet une étude focalisée d’une ligne perpendiculaire au plan échographique en fonction du temps. Le mode bidimensionnel permet de repérer les structures anatomiques et de sélectionner les lignes à explorer. Le mode temps-mouvement permet ensuite l’analyse des mouvements des structures anatomiques le long des lignes exploratoires.

2.3.1 Approche intercostale

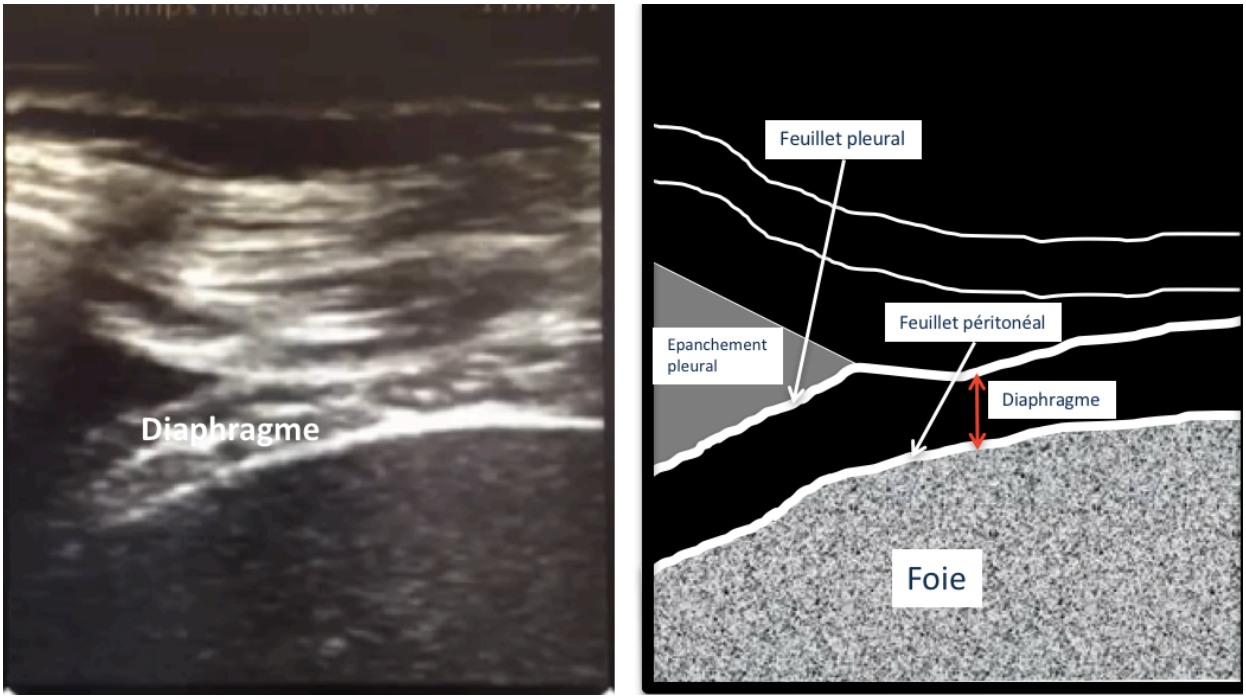
L’approche intercostale se situe au niveau de la zone d’apposition qui est la portion verticale du muscle, en contact avec la partie interne du gril costal (**Figure 6).**

Figure 6. Repérage échographique du diaphragme par l’approche intercostale (50).



Le diaphragme est localisé entre les feuillets péritonéal et pleural qui apparaissent hyperéchogènes. L’observation d’un feuillet échogène flottant entre les deux feuillets péritonéal et pleural est possible chez la majorité des sujets ; il s’agit d’un signe recherché par l’échographiste qui confirme le bon repérage du diaphragme.

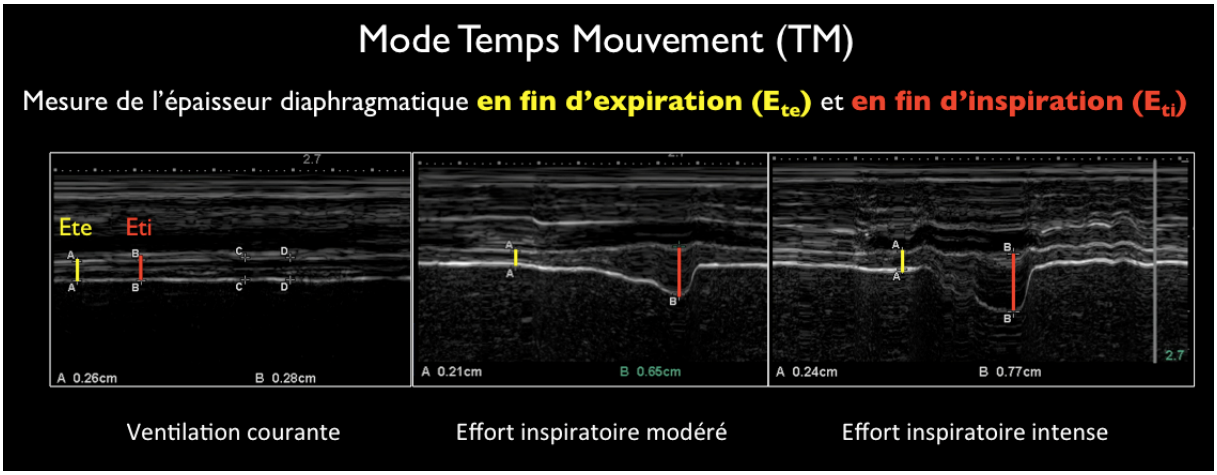
Figure 7. Représentation schématique des structures sus et sous diaphragmatiques à l'échographie intercostale



L'approche intercostale renseigne sur la structure anatomique du muscle par la mesure de son épaisseur en fin d'expiration (E_{te}) et au pic de l'inspiration (E_{ti}). L'analyse de l'épaisseur du diaphragme par l'approche intercostale nécessite un échographe muni d'une sonde linéaire de haute fréquence (8-13 MHz). Le diaphragme est visualisé en posant la sonde parallèlement à la ligne axillaire entre le 8ème et le 9ème espace intercostal. La sonde doit « regarder » le diaphragme perpendiculairement. Avec le mode B, le diaphragme est identifié comme une structure échogène constituée de trois feuillets superposés (**Figure 7**). Le mode M permet la visualisation au cours du temps des changements de l'épaisseur diaphragmatique induits par sa contraction. L'analyse fonctionnelle repose sur l'étude de l'épaississement du muscle. En effet, lors de sa contraction, le diaphragme s'épaissit et l'échographie peut alors mesurer la fraction d'épaississement (thickening fraction, TFdi). Le TFdi est obtenu en divisant la différence entre l'épaisseur télé-inspiratoire et télé-expiratoire

par l'épaisseur télé-expiratoire. Il est exprimé en pourcentage. Un TFdi inférieur à 20% en ventilation spontanée témoignerait d'une dysfonction diaphragmatique (51). La **Figure 8** illustre l'augmentation de l'épaisseur diaphragmatique en fin d'inspiration lors de la ventilation courante et lors d'efforts inspiratoires d'intensité modérée puis forte.

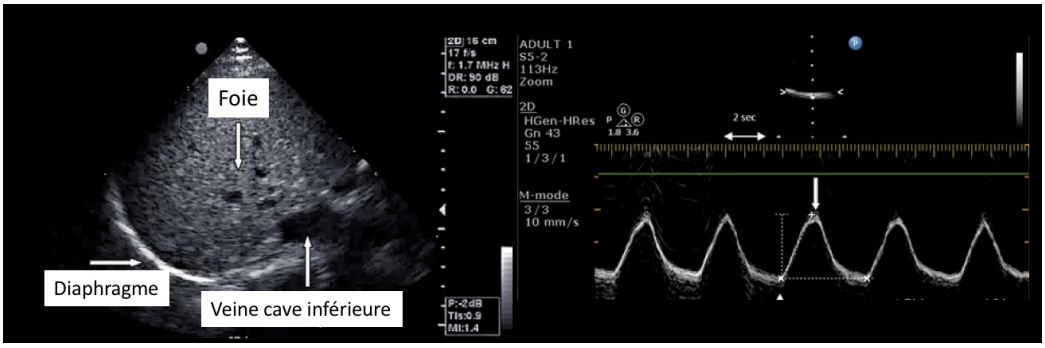
Figure 8. Visualisation échographique par l'approche intercostale de l'épaisseur du diaphragme dans différentes conditions de ventilation : repos, effort inspiratoire modéré et effort inspiratoire contre résistance (données personnelles).



2.3.2 Approche sous costale

L'approche sous costale visualise le dôme diaphragmatique séparant à proprement parler le thorax de l'abdomen, au centre duquel se trouve une zone tendineuse d'où rayonnent les fibres musculaires. L'approche sous costale analyse l'excursion du dôme. L'approche sous costale se fait au moyen d'une sonde basse fréquence (<5 MHz) de type « abdominale ». La sonde est positionnée sous le bord costal droit, perpendiculaire à la ligne médio claviculaire et dirigée vers le foie. En mode B, le diaphragme apparaît alors comme une ligne hyperéchogène diamétralement opposée à la sonde et entourant le foie **(Figure 9**).

Figure 9. Représentation schématique de l'approche échographie sous costale du diaphragme et de l'excursion diaphragmatique (D'après Matamis et coll. (50))



En mode M, la vitesse de balayage réglée au minimum permet de visualiser les cycles ventilatoires caractérisés par des excursions de la ligne de base : l'élévation de la ligne de base témoignant de l'éloignement du sommet du dôme de la sonde. Il est admis qu'une excursion diaphragmatique inférieure à 1 cm est en faveur d'une dysfonction diaphragmatique (48, 52).

2.4 Evaluation de la fonction diaphragmatique chez le patient sous ventilation mécanique

Pour les physiologistes qui s'intéressent au fonctionnement du diaphragme chez les patients de réanimation, le sevrage de la ventilation mécanique représente une condition expérimentale unique. La question du sevrage de la ventilation mécanique sera discutée ultérieurement en détails (voir *infra*). A ce stade, il est simplement nécessaire de mentionner que le sevrage de la ventilation est une étape cruciale dans la prise en charge d'un patient exposé à la ventilation mécanique. Par sevrage, on entend séparation du patient de son ventilateur. Pour être réalisée correctement, la phase de sevrage passe par une période où le patient « respire » de façon autonome, c'est à dire avec une assistance ventilatoire

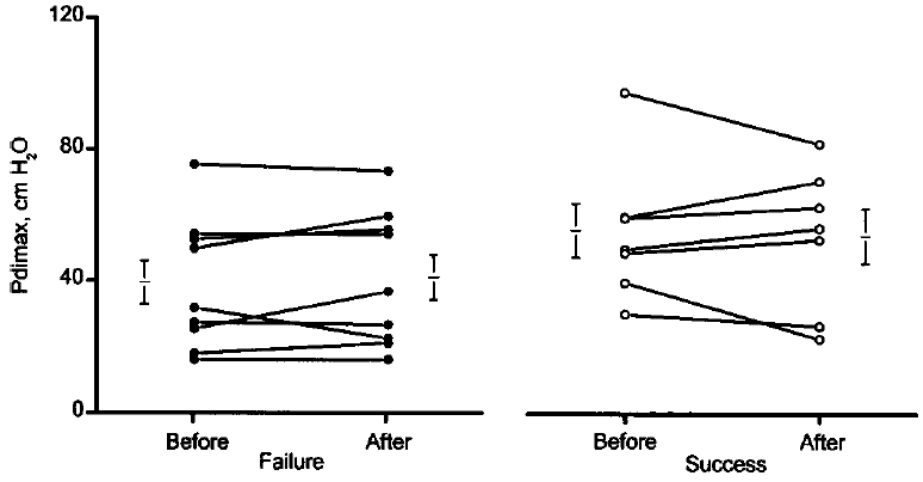
réduite ou nulle. Au cours de cette phase, la tolérance clinique du patient est observée. Cette tolérance dépend en très grande partie de l'intégrité de la fonction neuromusculaire des muscles respiratoires et notamment du diaphragme. Une question cruciale est de savoir si la survenue d'une fatigue musculaire peut affecter l'issue du sevrage. La fatigue musculaire est classiquement définie par l'incapacité temporaire et réversible pour un muscle squelettique à développer une force contractile pendant une durée déterminée (53). Une façon de quantifier cette fatigue est de mesurer le temps passé entre le début de la contraction jusqu'au temps où la force ne peut plus être soutenue. Par conséquent, pour répondre correctement à la définition, il est nécessaire de réaliser des mesures répétées de la force afin de démontrer sa diminution au cours du temps. En outre, après mise au repos, il est nécessaire de prouver la récupération de la force. Il semble donc évident que la mesure de la fatigue requiert une méthodologie complexe ce qui explique que peu de travaux soient disponibles en particulier chez les patients de réanimation. Les premiers travaux sur le sujet ont montré que pour le diaphragme humain, le temps nécessaire pour induire une fatigue est inférieur à 60 minutes quand la Pdi développée à chaque inspiration est supérieure à 40% de la Pdimax (53). Deux approches ont été développées pour mesurer la fatigabilité du diaphragme. Faisant le constat que le diaphragme a une activité cyclique et qu'il bénéficie par conséquent d'une période de relaxation à l'expiration, Grassino et Bellemare ont proposé d'utiliser le produit *Time Tension Index* (TTI) pour mesurer la fatigabilité du diaphragme (54). Ce produit est donné en multipliant le rapport du temps inspiratoire sur le temps total du cycle (Ti/Tot) par le produit de Pdi/Pdimax. Le TTI rend ainsi compte qu'à une fréquence respiratoire élevée, le diaphragme peut ainsi se fatiguer plus vite, la durée de la relaxation étant mathématiquement plus courte. Les auteurs ont montré chez le sujet normal une relation hyperbolique entre Ti/Ttot et Pdi/Pdimax et établi une valeur seuil de

TTdi entre 0,15 et 0,20 au-delà de laquelle la fatigue diaphragmatique survient. Un TTdi < 0,15 peut être soutenu indéfiniment sans apparition de fatigue.

L'application clinique de ce concept au cours du sevrage de la ventilation a été étudié par Vassilakopoulos et coll. (55). Ces auteurs ont mesuré le TTI chez 30 patients placés sous ventilation mécanique quelques heures après un échec de test de sevrage et quelques jours plus tard alors qu'ils venaient de réussir le test (55). L'intérêt de cette étude est d'avoir mesuré chez les mêmes patients l'évolution du TTI dans des conditions parfaitement différentes. Dans ce travail, les auteurs ont observé que le TTI était élevé après l'échec de sevrage (0,16) puis abaissé (0,10) au moment du succès. Ces résultats suggèrent que les patients en échec présentent une fatigue diaphragmatique ce qui n'était pas le cas au moment du succès, ce qui va dans le sens des travaux de Grassino et Bellemar. Toutefois, cette interprétation doit être pondérée car la valeur seuil de TTI de 0,15 au-delà de laquelle apparaît la fatigue, a été obtenue chez des sujets sains. Chez les patients de réanimation, les conditions de mesure sont différentes et il est vraisemblable que le seuil soit plus bas. Par ailleurs, un TTI élevé n'implique pas forcément l'existence d'une fatigue musculaire mais plus vraisemblablement cela indique que le sujet est à risque de développer une fatigue musculaire respiratoire qui va devenir patente dans un temps variable inversement proportionnel au TTI (54). Chez des patients de réanimation en échec de sevrage, il a été effectivement montré qu'une fatigue diaphragmatique n'est en réalité pas observée (56). Les signes cliniques de dysfonction diaphragmatique (avant la fatigue) sont précoces et conduisent généralement à ré-instituer le support ventilatoire avant la survenue d'une fatigue diaphragmatique. Ce résultat a été montré chez 19 patients prêts à débuter une épreuve de ventilation spontanée (56). Dans ce travail, Laghi et coll. ont mesuré avec la technique de stimulation des nerfs phréniques (permettant de s'affranchir de la motivation

des sujets), la fonction et la fatigabilité diaphragmatique (Pdimax et TTI) au début et à la fin d'une épreuve de ventilation spontanée. Le premier résultat était que les valeurs de Pdimax n'étaient pas significativement différentes entre le début et la fin de l'épreuve de ventilation, en particulier chez les patients présentant un échec de l'épreuve de ventilation spontanée (**Figure 10**). L'autre résultat était que l'index de fatigabilité (TTI) augmentait significativement entre le début et la fin de l'épreuve de ventilation spontanée mais cette augmentation était présente dans les deux groupes, succès comme échec. La conclusion des auteurs était que les patients échouant à une épreuve de ventilation spontanée ne présentaient pas de fatigue diaphragmatique (56). Comme indiqué plus haut, l'explication la plus vraisemblable est que la ventilation mécanique était ré-instituée trop tôt (pour le bien des patients) pour observer des signes de fatigue diaphragmatique.

Figure 10. Mesure de la pression transdiaphragmatique maximale mesurée en réponse à la stimulation phrénique (Pdimax) chez des patients en échec et réussissant une épreuve de ventilation spontanée (avant et après). D'après Laghi et coll (56).



Une autre méthode a été utilisée pour mesurer la fatigue diaphragmatique. Il s'agit de recueillir le spectre de l'activité EMG du diaphragme au cours d'un exercice et de

quantifier la fréquence du signal. L'index H/L est le rapport entre les fréquences rapides et les fréquences lentes d'un signal EMG brut du diaphragme. La diminution de ce rapport est corrélée à l'apparition de la fatigue diaphragmatique (57).

L'index H/L et le TTI sont des outils performants mais qui sont difficiles à utiliser en routine. A ce titre, des indices alternatifs ont été développés. Plus accessibles, ces indices ont indéniablement permis la popularité de l'évaluation de la fonction respiratoire au moment du sevrage mais ils connaissent comme inconvénient majeur de ne pas rendre compte du fonctionnement spécifique du diaphragme.

Le premier de ces indices est l'indice de polypnée superficielle proposé par Tobin et Jang en 1991 (58). Cet indice est calculé en faisant le rapport de la fréquence respiratoire sur le volume courant moyen obtenu par un spiromètre pendant une minute après avoir déconnecté le patient du ventilateur. Ce rapport rend compte de l'adaptation du profil ventilatoire à la ventilation spontanée. Peu élevé (classiquement inférieur à 105 cycles.l^{-1}), il prédit le succès du sevrage (test de ventilation spontanée suivi d'extubation) (58).

Plus tard, le même groupe a étudié l'évolution du PTP et des propriétés mécaniques pulmonaires au cours du sevrage (59). Les auteurs ont observé que des patients porteurs d'une broncho-pneumopathie chronique obstructive en échec de sevrage présentaient de façon prédominante une augmentation de l'élastance pulmonaire, des résistances et du PTP entre le début et la fin de l'épreuve de ventilation spontanée (59). Comparativement aux patients réussissant le sevrage, l'élastance augmentait significativement plus mais l'augmentation du PTP au cours de l'épreuve de ventilation spontanée était présente dans les deux groupes. Ces résultats suggèrent que l'échec de sevrage s'accompagne principalement d'une altération des propriétés mécaniques pulmonaires sans défaillance de

la capacité des muscles à générer une pression. Par conséquent, la mesure du PTP au cours du sevrage ne semble pas intéressante pour en prédire l'issue.

La mesure de la pression inspiratoire maximale a également été proposée pour évaluer la force du système respiratoire et prédire l'issue du sevrage (58–60). Sahn et Lakshminarayan ont été les premiers à proposer une valeur de pression inspiratoire maximale de - 30 cmH_2O au-dessus de laquelle les patients étaient sevrés avec succès tandis que les patients incapables de produire des valeurs supérieures à - 20 cmH_2O étaient associées à l'échec (61). Toutefois, ces valeurs n'ont pas été confirmées par la suite (58–61). En pratique, la pression inspiratoire maximale est plus utile pour comprendre les raisons de l'échec (faiblesse musculaire) que pour prédire l'issue du sevrage.

Les travaux discutés ici rendent compte que les deux principaux déterminant du succès du sevrage sont 1) la balance charge/capacité du système neuro-ventilatoire et 2) le profil ventilatoire adopté lors de la transition vers la ventilation spontanée (55, 59, 62, 63). L'exploration de la fonction diaphragmatique dans la perspective de comprendre les raisons d'un échec de sevrage est donc fondamentale. Le développement d'outils fiables, spécifiques et facilement accessibles est par conséquent un enjeu important dans ce contexte.

2.4.1 Utilisation de l'échographie diaphragmatique en réanimation

L'utilisation de l'échographie pour analyser la structure et la fonction diaphragmatique en réanimation connaît un enthousiasme croissant depuis quelques années (50, 64). Le premier travail réalisé en réanimation a utilisé l'excursion diaphragmatique pour diagnostiquer une dysfonction diaphragmatique chez des patients de post chirurgie cardiaque, la mesure de la pression transdiaphragmatique tenant lieu de mesure de référence (52). L'échographie a par la suite été utilisée pour identifier les patients

à risque d'échec de sevrage de la ventilation mécanique, initialement par la mesure de l'excursion (48, 49, 65) et plus récemment par la mesure du TFdi (46, 47). Il est important de souligner que le TFdi dépend fortement du niveau d'assistance ventilatoire chez le patient ventilé (43, 45) et très vraisemblablement de l'intensité de la commande ventilatoire centrale. L'échographie montre aussi son intérêt en réanimation par sa capacité à mesurer l'épaisseur diaphragmatique. Une étude a montré, chez sept patients de réanimation exposés à la ventilation mécanique, une diminution progressive de l'épaisseur du diaphragme (42), laquelle pourrait être compatible avec l'atrophie rapportée par les travaux histologiques portant sur la dysfonction diaphragmatique induite par la ventilation mécanique (66, 67). Ce résultat a été confirmé par deux autres études de cohorte (68, 69). En réanimation, l'étude de la fonction du diaphragme par l'échographie pourrait être une alternative intéressante à la technique de stimulation des nerfs phréniques qui reste la technique de référence. Néanmoins, une telle comparaison n'a jamais été encore réalisée et fera l'objet du deuxième travail de cette thèse.

3. Dysfonction diaphragmatique en réanimation

En réanimation, le diaphragme fait l'objet de plusieurs agressions successives dont les mécanismes et les implications sont bien différents (36). Chronologiquement, la première de ces deux agressions survient à la phase toute initiale du séjour ou préalablement à l'admission. Au même titre que la neuromyopathie de réanimation (70, 71), la dysfonction diaphragmatique est d'origine multifactorielle. Elle est déterminée par l'intensité et la sévérité de la maladie conduisant le patient en réanimation. Lors de cette première agression, le diaphragme semble dysfonctionner au même titre que tout autre organe. Elle s'intègre ainsi à la défaillance multi-viscérale compliquant les agressions sévères. La seconde de ces agressions survient dans un second temps et semble être principalement induite par la ventilation mécanique « prolongée ». Elle porte le nom de dysfonction diaphragmatique induite par la ventilation mécanique (72).

3.1 Dysfonction diaphragmatique à l'admission

Cette dysfonction est retrouvée dès l'admission du patient. Elle semble résulter de l'agression initiale ayant entraîné la défaillance d'organe motivant le transfert en réanimation. La dysfonction diaphragmatique associée au sepsis en est le principal modèle (73). Le mécanisme sous-jacent à cette dysfonction est une atteinte intrinsèque du muscle (74). Vingt-quatre heures après leur intubation, près de deux tiers des patients de réanimation présentaient une dysfonction diaphragmatique (35). Les deux facteurs prédictifs indépendants de cette dysfonction sont la sévérité du patient à l'admission en réanimation et la présence d'un sepsis, ce qui va dans le sens des modèles animaux. Enfin, la présence d'une dysfonction diaphragmatique est corrélée à la mortalité en réanimation (35). Ces données suggèrent que chez l'humain, le diaphragme, au même titre que tout organe, peut

présenter une défaillance en réponse à l'agression qui conduit le patient en réanimation. Cette défaillance diaphragmatique, en s'ajoutant aux autres défaillances d'organe, a un impact sur le pronostic. De façon intéressante, une étude ancillaire réalisée à partir de cette cohorte, a montré que chez 9/23 (39%) patients qui présentaient une dysfonction diaphragmatique initiale, la fonction diaphragmatique s'améliorait au cours du séjour (75). Ce résultat évoque l'hypothèse d'une réversibilité de ce mécanisme lié au sepsis au même titre que le mécanisme de dysfonction myocardique lié au sepsis (76). D'autres agressions précoces sont susceptibles de participer à l'altération de la fonction diaphragmatique chez les patients de réanimation. L'état de choc cardiogénique (77), l'acidose respiratoire (78), la chirurgie abdominale (79) et certains médicaments comme les curares et les corticostéroïdes sont des facteurs de risque reconnus de dysfonction diaphragmatique dans les modèles expérimentaux. Du fait de leur présence potentiellement simultanée chez les patients de réanimation, leur contribution respective est difficilement quantifiable.

3.2 Dysfonction diaphragmatique induite par la ventilation mécanique

Il est bien établi que la ventilation contrôlée s'accompagne d'une altération temps dépendante des propriétés contractiles du diaphragme (80, 81). Ce phénomène a principalement été montré chez l'animal, mais on dispose depuis peu de données chez l'humain (34, 66, 82). Comme pour la neuromyopathie de réanimation, la principale difficulté des travaux effectués sur le diaphragme des patients de réanimation réside dans l'impossibilité de quantifier la contribution de la ventilation mécanique sur la survenue de la dysfonction. En effet, les patients de réanimation sont exposés à de multiples agressions dont la ventilation mécanique ne représente qu'un aspect parmi d'autres. L'autre difficulté est de pouvoir analyser la contractilité du diaphragme in vivo en réanimation ce qui nécessite des techniques d'investigation inenvisageables en dehors du périmètre de certains

centres experts. La première étude ayant étudié histologiquement le diaphragme chez l'humain est pédiatrique à partir de prélèvements d'autopsies (83). Dans ce travail, les auteurs ont montré une atrophie des fibres I et II diaphragmatiques chez des enfants ventilés artificiellement pendant plusieurs jours. Plus récemment, en faisant l'hypothèse que l'atrophie diaphragmatique représente un marqueur pertinent de dysfonction (ce qui est le cas dans la plupart des études animales) et en étudiant des patients en état de mort encéphalique (moins exposés que les autres patients de réanimation aux autres types d'agression), Levine et coll. ont montré qu'une ventilation mécanique contrôlée prolongée est associée à un haut degré d'atrophie des fibres musculaires du diaphragme (66). Le diaphragme est alors le siège d'altérations structurelles (34) ainsi que d'une nette élévation des marqueurs de protéolyse musculaire et du niveau d'agression oxydante (34) qui ne sont pas observés dans muscle pectoral ni dans le muscle dorsal latéral (66, 84). La plupart des informations concernant la contractilité du diaphragme des patients faisant l'objet d'une ventilation mécanique d'au moins 48 heures émane d'études réalisées sur de petits effectifs (34, 82). Dans leur ensemble, ces études suggèrent que la ventilation mécanique s'associe, chez l'humain, à une dysfonction diaphragmatique, cette altération semble être temps dépendante.

4. Diaphragme et Sevrage de la ventilation mécanique en réanimation

La ventilation mécanique est une technique de suppléance d'organe mise en place à l'occasion d'une insuffisance respiratoire aiguë, d'une défaillance multiviscérale ou pour la protection des voies aériennes supérieures. Développée au cours des années cinquante pendant l'épidémie de poliomyélite aiguë au Danemark, elle est avec la dialyse, à l'origine de la Médecine Intensive – Réanimation en tant que discipline à part entière telle qu'elle est connue de nos jours. Les bénéfices de la ventilation mécanique sont bien montrés (85). Ceux-ci sont particulièrement observés au cours de la prise en charge des nombreuses étiologies de l'insuffisance respiratoire aiguë (pneumonies bactériennes et virales, décompensation des maladies chroniques respiratoires, œdème aigu pulmonaire, syndrome de détresse respiratoire aiguë), des comas pour la protection des voies aériennes supérieures et des états de choc qui associent défaillance circulatoire et respiratoire. Toutefois, la ventilation mécanique doit être vue davantage comme un traitement d'attente que comme un traitement curatif en tant que tel. En dépit de ses aspects bénéfiques, la ventilation mécanique expose les patients à des complications inhérentes à son utilisation (pneumonies acquises sous ventilation mécanique, lésions alvéolaires induites par la ventilation, complications du décubitus). Pour cette raison, un des objectifs principaux des équipes soignantes est de pouvoir séparer le plus tôt possible et en toute sécurité les patients de leur ventilateur. Ce processus, crucial, est connu sous le terme de sevrage de la ventilation mécanique. Si la grande majorité des patients peut être séparée du ventilateur sans difficulté, le sevrage peut s'avérer compliqué chez une petite proportion d'entre eux mais qui représente une importante morbi-mortalité. On parle d'échec de sevrage lorsque la séparation du ventilateur n'est pas possible.

4.1 Définitions et classification du sevrage de la ventilation mécanique

La détermination du moment le plus adéquat pour séparer en toute sécurité un patient du ventilateur n'est pas aisée et représente un réel défi dans la pratique clinique. Sevrés trop tôt, les patients sont exposés au risque d'échec d'extubation et à ses conséquences sur la morbi-mortalité (86) ; trop tard, ils sont exposés aux complications de la ventilation mécanique et du décubitus prolongé (87). Le processus de sevrage de la ventilation mécanique est relativement bien standardisé et comporte trois étapes : 1) l'identification de critères prérequis à la réalisation de l'épreuve de ventilation spontanée ; 2) la réalisation de l'épreuve de ventilation spontanée et 3) la décision d'extubation (88). La première étape vise à n'entreprendre l'épreuve de ventilation spontanée que chez des patients susceptibles d'être finalement extubés. Les critères prérequis permettent ainsi de s'assurer de la pertinence de la réalisation de l'épreuve de ventilation spontanée et par conséquent d'éviter la réalisation d'une procédure inutile et potentiellement anxiogène. Ces critères relativement simples assurent que le patient est stable sur le plan hémodynamique, qu'il a un niveau d'éveil autorisant théoriquement l'extubation et que le profil respiratoire n'est pas déjà suractivé avant de tester la tolérance à la ventilation spontanée.

Si les critères prérequis sont présents, il convient de réaliser le plus tôt possible une épreuve de ventilation spontanée. L'épreuve de ventilation spontanée a pour objectif principal de mettre le patient dans une situation reproduisant le plus fidèlement possible les conditions de l'extubation afin d'évaluer la tolérance clinique induite par cette transition. Il s'agit d'une étape cruciale bien qu'intermédiaire dans le processus décisionnel visant à extuber le patient [6]. L'extubation, étape ultime du processus de sevrage puisqu'elle consiste au retrait de la sonde d'intubation est une période à risque pour certains patients. L'échec d'extubation, défini généralement par le recours à une nouvelle intubation dans un

délai de 48 heures à sept jours, est associé à de nombreuses complications dont plusieurs études de cohortes suggèrent qu'elles influencent de façon significative le pronostic. Epstein et coll. ont ainsi rapporté que la réintubation était significativement associée à une surmortalité chez les patients réintubés (43% vs 12% chez les patient non réintubés) et ce, indépendamment de l'étiologie de l'échec d'extubation (89, 90). Ce résultat a été confirmé par une autre étude montrant que l'échec d'extubation était plus fréquent lorsque l'extubation était accidentelle plutôt que programmée mais que les conséquences étaient tout aussi délétères sur le pronostic des patients (86).

4.2 Mécanismes de l'échec du sevrage

Divers mécanismes physiopathologiques, parfois intriqués, peuvent être à l'origine de l'échec de sevrage (91). Schématiquement, ces causes sont liées à un déséquilibre entre la capacité et la charge imposée au système cardio-pulmonaire et neuro-ventilatoire (92). Les causes de diminution de la capacité du système respiratoire et les causes d'augmentation de la charge respiratoire sont listées de façon non exhaustive dans le **Tableau 2**.

Tableau 2. Causes de diminution de la capacité respiratoire et causes d'augmentation du travail respiratoire. Adapté de (92).

Causes de diminution de la capacité respiratoire	Causes d'augmentation de la charge respiratoire
Par dépression de la commande centrale	***Par augmentation de la charge élastique***
Sédation	Œdème pulmonaire
Alcalose métabolique,	Déformation thoracique (cyphoscoliose)
Lésions neurologiques centrales	Pneumonie, atélectasie
	Pression télé-expiratoire positive intrinsèque élevée
Par diminution de la conduction du signal	Distension abdominale, ascite, obésité
Motoneurone (SLA)	***Par augmentation de la charge résistive***
Racines nerveuses (SGB)	
Neuropathie de réanimation	Bronchospasme, sécrétions bronchiques
	Sonde d'intubation obstruée, petit diamètre
Par diminution de la force musculaire	
Amyotrophie	**Par augmentation de la ventilation minute :**
Métabolique (diminution des niveaux de P/Mg/Ca/K)	Anomalie métabolique
	Shunt intrapulmonaire, augmentation de l'espace mort

SLA : sclérose latérale amyotrophique ; SGB : syndrome de Guillain-Barré ; P : phosphore ; Mg : magnésium ; Ca : Calcium ; K : potassium.

La charge imposée dépend des propriétés mécaniques des structures composant l'appareil respiratoire : voies aériennes supérieures, parenchyme pulmonaire et paroi thoracique. La résistance des voies aériennes peut être augmentée lorsqu'il existe une maladie respiratoire obstructive avec mucosités bronchiques et sécrétions excessives. Presque toutes les affections du parenchyme (œdème pulmonaire, pneumonie ou atélectasie mais pas l'emphysème centro-lobulaire) sont susceptibles d'affecter les propriétés élastiques de l'appareil respiratoire et d'en réduire la compliance, participant alors à l'augmentation de la charge respiratoire élastique. La charge élastique peut être sévèrement augmentée en cas d'obstruction bronchique avec pression télé-expiratoire positive intrinsèque. La distension dynamique en est une conséquence directe. Elle est

générée par un effet de piégeage (l'air entre mais ne sort pas). Une partie de l'effort inspiratoire est utilisée pour lutter contre et compenser la pression télé-expiratoire positive intrinsèque avant de générer du volume courant, ce qui représente un coût énergétique important mais inutile en terme de ventilation alvéolaire efficace. Le déséquilibre peut survenir lorsque la capacité du système respiratoire est insuffisante. Cette éventualité est rencontrée notamment en cas de neuromyopathie de réanimation. Bien qu'il n'existe pas de données précises dans la littérature sur leur implication respective, les causes d'échec de sevrage sont multiples (91). Outre la dysfonction cardiaque induite par la transition en ventilation spontanée qui est une cause fréquente et traitable (93), d'autres causes sont identifiées telles que les maladies du parenchyme pulmonaire, l'augmentation des résistances des voies aériennes, les perturbations métaboliques (91) ou encore la présence d'un délirium (94). Enfin, les anomalies de la chaîne neuro-musculaire sont fréquement impliquées dans l'échec du sevrage. Le travail de cette thèse s'intéressera particulièrement à cette dernière cause.

Cause neuro- musculaire

L'échec de sevrage peut résulter d'une lésion présente sur l'ensemble de la chaîne de commande neuromusculaire respiratoire du signal nerveux. Dans le sens descendant, cela comprend une lésion du cortex ou du tronc cérébral, des motoneurones, des racines nerveuses et des muscles respiratoires. Certaines affections sont présentes avant l'admission en réanimation et peuvent précipiter à ce titre le recours à la ventilation mécanique. Il s'agit par exemple des accidents vasculaires cérébraux ou du syndrome de Guillain-Barré. D'autres sont induites par le séjour en réanimation et vont compliquer le sevrage de la ventilation. On trouve dans cette catégorie notamment la dysfonction diaphragmatique induite par la ventilation mécanique.

Au niveau du système nerveux central, une encéphalite ou un accident vasculaire cérébral hémorragique ou ischémique sont des causes de dépression de la commande ventilatoire à l'origine d'une hypoventilation alvéolaire aigue lors de la réalisation de l'épreuve de ventilation spontanée (91). Le recours à la sédation chez le malade sous ventilation mécanique peut avoir les mêmes conséquences, justifiant pour certains auteurs le recours à des protocoles d'interruption quotidienne de la sédation dans la perspective de faciliter la réalisation de l'épreuve de ventilation spontanée et de raccourcir la durée du sevrage de la ventilation mécanique (95). A l'étage du motoneurone, la maladie la plus remarquable a été le virus de la poliomyélite qui a donné naissance à la ventilation mécanique par Ibsen au Danemark au cours de l'épidémie du milieu du vingtième siècle (96). De nos jours, l'atteinte la plus fréquente du motoneurone est dégénérative, il s'agit de la sclérose latérale amyotrophique. Au niveau de la plaque de transmission neuromusculaire, la crise aigue myasthénique est une atteinte pouvant être révélée de novo à l'origine d'une insuffisance respiratoire aiguë. Par la suite, elle peut aussi donner lieu à des difficultés de sevrage de la ventilation. Enfin, l'admission en réanimation, sa cause, sa sévérité et les traitements ayant été nécessaires sont susceptibles d'induire une neuromyopathie dite « de réanimation » (97). La traduction clinique de la neuromyopathie de réanimation est évidente lorsqu'elle touche les nerfs et muscles des membres avec un tableau de quadri-parésie pouvant être complet (70). En revanche, l'atteinte du diaphragme et des muscles respiratoires est moins facilement détectable. Plusieurs travaux ont déjà rapporté une association entre une atteinte globale des muscles respiratoires (pas spécifiquement du diaphragme) et une prolongation de la durée de ventilation mécanique liée à un sevrage difficile (98, 99). En dépit du niveau de preuve croissant sur le rôle crucial de la dysfonction diaphragmatique au cours du sevrage de la ventilation mécanique, les méthodes

d’investigation de la fonction diaphragmatique non invasives et facilement accessibles manquent encore, ce qui explique en partie la méconnaissance des enjeux de ce phénomène (100).

5. Relation entre neuromyopathie de réanimation, dysfonction diaphragmatique et sevrage de la ventilation mécanique

La survenue d'un déficit moteur – pouvant atteindre le stade de la paralysie – réversible, chez des patients de réanimation par ailleurs intacts sur le plan des fonctions supérieures et présentant une quasi-aréfléxie tendineuse a été décrite pour la première fois en 1956 (101). Depuis, les nombreuses publications sur le sujet ont déterminé que la neuromyopathie de réanimation est une affection fréquente touchant près de 25% des patients exposés à la ventilation mécanique (102, 103). Il s'agit de la plus fréquente des maladies neuromusculaires rencontrées en réanimation (71, 104). Cette prévalence élevée résulte de deux phénomènes : 1) une meilleure identification de la maladie liée à l'amélioration des connaissances et des moyens d'investigations ; et 2) une amélioration de la survie des patients les plus sévères, c'est à dire des patients les plus à risque de développer la maladie. La neuromyopathie de réanimation peut atteindre le système neuromusculaire périphérique à tous ses étages : axone, transmission, excitation musculaires et myocyte lui-même. Il a été suggéré que l'atteinte diaphragmatique soit intégrée à cette affection pour n'en représenter qu'un aspect du tableau clinique global (105). Toutefois, comme nous le verrons plus tard, bien que cette hypothèse soit séduisante sur de nombreux aspects, elle fait l'objet de contre arguments. La physiopathologie de la neuromyopathie de réanimation associe des anomalies musculaires et axonales susceptibles d'être associées. Au niveau musculaire, une atrophie et une perte des filaments épais de myosine sont présent comme en témoignent les travaux réalisés sur le muscle exposé au sepsis chez l'animal (106). Au niveau axonal, Latronico et coll. ont décrit les lésions axonales et démyelinisantes (70). Cliniquement, l'affection est suspectée devant une faiblesse musculaire homogène touchant les quatre membres. Le diagnostic de neuromyopathie de

réanimation est réalisé en utilisant l'échelle du Medical Research Score (MRC) qui évalue la force musculaire de douze muscles (trois muscles à chacun des membres, soit 12 muscles au total), de 0 (aucune force) à 5 (force normale). Le score maximal est donc de 60. Un seuil inférieur à 48 définit une neuromyopathie de réanimation. Bien que ce score soit associé à une bonne reproductibilité (102) et soit facilement réalisable, il nécessite la coopération du sujet ce qui limite sa généralisation. Ceci explique pourquoi le diagnostic de neuromyopathie est détecté tardivement lorsque le patient redevient conscient. En cas de présentation inhabituelle, la technique de référence repose sur l'électroneuromyogramme (107).

L'identification des facteurs de risque de neuromyopathie de réanimation n'est pas facile chez le patient de réanimation souvent exposés à de multiples agressions, chacune potentiellement impliquée dans la survenue de l'affection (108). Les deux facteurs de risque reconnus comme étant fortement impliqués sont la défaillance multiviscérale (74,89,90) et l'immobilisation (103, 112). Le sepsis comme cause de défaillance multiviscérale est le modèle le plus étudié, si bien qu'il est difficile de distinguer qui de la défaillance ou du sepsis intervient majoritairement. L'immobilisation quant à elle est souvent indissociablement liée à la durée de ventilation mécanique dans les études, ce qui là aussi complique la mesure de la contribution respective de chacun des phénomènes. La responsabilité d'autres facteurs de risque tels que l'hyperglycémie (88,97), l'utilisation des curares et des corticostéroïdes est vraisemblable mais le niveau de preuve qui leur est associé est plus faible (108).

La présence d'une neuromyopathie de réanimation a une importance considérable sur le pronostic. Les patients chez lesquels une neuromyopathie de réanimation est mise en évidence ont une surmortalité en réanimation et à l'hôpital (102, 103, 111, 112). Les causes de cette surmortalité pourraient être liées à une prolongation de la durée de ventilation mécanique exposant les patients à davantage de complications nosocomiales. Toutefois,

dans les études ayant établi une association entre neuromyopathie de réanimation et augmentation de la durée de ventilation mécanique (98, 111, 112, 115), il n'est pas possible de distinguer l'effet de la neuromyopathie sur l'augmentation de la durée de ventilation de l'impact de la ventilation prolongée elle-même sur la survenue de la neuromyopathie. Compte tenu la prévalence élevée de la neuromyopathie de réanimation chez les patients exposés à un sevrage difficile (98, 111), il est légitime de s'interroger sur la relation entre les deux phénomènes. Les patients ayant des difficultés de sevrage de la ventilation mécanique ont-ils des difficultés du fait de la présence d'une neuromyopathie (connue ou méconnue) ou est-ce les difficultés de sevrage (et le prolongement de la durée de ventilation mécanique) qui favorisent la survenue de la neuromyopathie ? Les nerfs phréniques et le diaphragme sont-ils également touchés par la neuromyopathie de réanimation au même titre que les nerfs et muscles périphériques ? Plusieurs arguments plaident en effet pour une atteinte synchrone, locomotrice et diaphragmatique. Premièrement, il existe une association entre la présence d'une neuromyopathie de réanimation et une diminution de la force musculaire respiratoire (98). Deuxièmement, la présence d'une neuromyopathie de réanimation, au même titre que la diminution de la force musculaire respiratoire, est associée à des difficultés de sevrage et à une augmentation de la durée de ventilation mécanique (98, 111, 115). Troisièmement, les deux entités partagent des facteurs de risque communs comme la sévérité initiale et la durée de ventilation mécanique. Pourtant, à la grande différence des autres muscles, le diaphragme, à l'exception du myocarde, est le seul à ne jamais voir son activité s'interrompre au cours du fonctionnement physiologique, de la naissance au décès. Il est donc vraisemblable qu'une mise au repos plus ou moins complète d'un muscle non physiologiquement programmé pour connaître une interruption de son activité ait des conséquences sur son fonctionnement. Il est tout aussi vraisemblable que ces

conséquences soient différentes sur d'autres groupes musculaires moins sensibles aux effets du repos forcé. Ceci est suggéré par des données montrant que le repos induit par la ventilation mécanique induit une atrophie diaphragmatique qui n'est pas observée sur le muscle pectoralis ou le muscle dorsal latéral (66, 84). Enfin, l'association qui a été rapportée entre l'atteinte musculaire locomotrice et l'atteinte musculaire respiratoire avec les difficultés de sevrage n'a pas pris en compte spécifiquement la fonction diaphragmatique (98). En réalité, aucune étude n'a rapporté une telle association en étudiant spécifiquement la fonction diaphragmatique. L'association entre force musculaire et difficultés de sevrage a été réalisée en étudiant la fonction globale des muscles respiratoires, et non spécifiquement du diaphragme. La présence et l'implication de la dysfonction diaphragmatique dans les difficultés de sevrage d'un patient présentant par ailleurs une neuromyopathie de réanimation semble logique mais elle n'est pas démontrée à ce jour.

6. Rôle de la dysfonction diaphragmatique dans l'échec du sevrage de la ventilation mécanique

Quelle qu'en soit la raison, il est intuitif de mettre en relation la dysfonction diaphragmatique et l'échec du sevrage. Une réduction de la contractilité du diaphragme, principal muscle inspiratoire est susceptible d'affecter la balance charge/capacité du système neuro-ventilatoire déterminant principal du succès du sevrage (92). A ce titre, la présence d'une dysfonction diaphragmatique chez le patient placé sous ventilation mécanique entreprenant une épreuve de ventilation spontanée a été rapportée par plusieurs auteurs (48, 49, 52). Certaines procédures chirurgicales comme la chirurgie cardiaque sont particulièrement à risque de survenue d'une dysfonction diaphragmatique et ont constitué les modèles des premières observations (52, 116). La dysfonction diaphragmatique gauche dans ce contexte survient lors de l'utilisation de l'artère mammaire interne gauche pour les pontages aorto-coronariens. Les lésions surviennent directement lors de la dissection du vaisseau situé à proximité du nerf phrénique. La survenue d'une dysfonction diaphragmatique droite est également rapportée lors des dissections difficiles de l'oreillette droite et de la veine cave inférieure. Une dysfonction diaphragmatique peut également survenir dans les contextes post opératoires en dehors de la chirurgie cardiaque, lors des interventions de chirurgie digestive ou thoraciques extra cardiaques mais sans lésion directe du nerf phrénique (79, 117). Cette dysfonction est la conséquence d'un défaut de contractilité, dont l'étiologie est multifactorielle : atteinte pariétale, douleur post opératoire et modification du régime ventilatoire liée à une diminution des volumes pulmonaires. Chez les patients de chirurgie cardiaque exposés à un sevrage prolongé, une dysfonction diaphragmatique est retrouvée de façon quasi systématique (52, 116) et est associée à la survenue de complications graves et potentiellement létales (116). Chez des patients de

réanimation non exposés à une chirurgie, une dysfonction diaphragmatique est retrouvée par échographie chez 29% d'entre eux et est associée à une augmentation de la durée du sevrage (48). Cette prévalence est proche de celle retrouvée dans deux autres études ayant étudié la fonction diaphragmatique par l'échographie au cours du sevrage (49, 118). Dans un travail plus récent (119), la fonction diaphragmatique était analysée avec la technique de référence (la stimulation des nerfs phréniques) dans une population sélectionnée puisqu'il s'agissait de patients présentant une neuromyopathie de réanimation définie par un score MRC inférieur à 48 (103). Dans cette population, une dysfonction diaphragmatique était retrouvée chez 80% des patients aptes à débuter le sevrage de la ventilation mécanique (119). Un autre travail utilisant la stimulation des nerfs phréniques a été réalisé chez 16 patients et a rapporté une prévalence de la dysfonction diaphragmatique au moment du sevrage de 75% (56). Les cinq études ayant rapporté la prévalence de la dysfonction diaphragmatique au moment du sevrage sont présentées dans le **Tableau 3**.

Tableau 3. Prévalence de la dysfonction diaphragmatique selon la technique diagnostique au moment du sevrage de la ventilation mécanique

Etudes	**Prévalence**
Avec l'échographie comme outil diagnostic	
Kim et al. (48)	24/82 (29%)
Jiang et al. (49)	20/55 (36%)
Lu et al. (118)	14/41 (34%)
Avec la stimulation des nerfs phréniques comme outil diagnostic	
Jung et al. (119)	32/40 (80%)
Laghi et al. (56)	12/16 (75%)

Il est frappant de constater une différence du simple au double dans la prévalence de la dysfonction diaphragmatique selon la technique d'investigation utilisée. Cette différence doit être pondérée par deux considérations. La première est que la technique de stimulation phrénique surestime vraisemblablement la prévalence de la dysfonction diaphragmatique. La seconde est qu'à ce jour, il n'existe pas de définition reconnue de la dysfonction diaphragmatique. On peut toutefois retenir que la dysfonction diaphragmatique est vraisemblablement sous diagnostiquée au moment du sevrage et qu'elle influence de manière significative l'issue du sevrage. Sans étudier spécifiquement le diaphragme, il est possible d'étudier des indices globaux de la fonction musculaire respiratoire (pression inspiratoire maximale, pression expiratoire maximale). Une étude a rapporté une association significative entre une diminution de la pression inspiratoire maximale, une diminution de la pression expiratoire maximale et une diminution de la capacité vitale d'une part et une augmentation de la durée du sevrage d'autre part (98). De façon intéressante, la dysfonction des muscles respiratoires était également fortement corrélée à la présence d'une atteinte locomotrice (98). Ces résultats suggèrent que les propriétés contractiles des muscles respiratoires dans leur ensemble, et non uniquement du diaphragme, sont négativement impactées par le séjour en réanimation.

Position du problème

Le diaphragme en tant que principal muscle inspiratoire joue un rôle majeur dans l'issue du sevrage de la ventilation mécanique. Pour cette raison, l'exploration de la fonction diaphragmatique est devenue l'objet de nombreux efforts de recherche. La complexité principale de cette exploration réside dans la difficulté de disposer d'une méthode non invasive, fiable, facilement disponible et reproductible chez des patients placés sous ventilation mécanique, non transportables dans les services d'explorations fonctionnelles et souvent non coopératifs. Plusieurs travaux ont rapporté un impact délétère de la dysfonction diaphragmatique détectée au moment de l'épreuve de ventilation spontanée sur l'issue du sevrage. Ces travaux ont été réalisés avec l'échographie diaphragmatique qui n'est pas la technique de référence ou chez des populations très sélectionnées comme en post opératoire de chirurgie cardiaque. Par ailleurs, l'atteinte locomotrice de la neuromyopathie de réanimation a également un impact péjoratif sur l'issu du sevrage et ces deux atteintes, diaphragmatique et locomotrice, semblent partager des facteurs de risque communs comme la durée de ventilation mécanique et la présence d'un sepsis. Il apparaît donc nécessaire de déterminer précisément quels sont les facteurs de risque de chacune des atteintes et si la coexistence des deux atteintes chez un même patient est fréquente. Cela permettrait d'étudier séparément le rôle respectif de la neuromyopathie de réanimation et de la dysfonction diaphragmatique dans le pronostic des patients de réanimation. Enfin, de nouveaux indices obtenus par l'échographie et l'électromyographie du diaphragme pourraient se révéler intéressants dans l'étude des mécanismes d'échec du sevrage de la ventilation.

Hypothèses

L'argumentaire développé ci-dessus témoigne de l'importance que revêt la dysfonction diaphragmatique dans la prise en charge des patients de réanimation placés sous ventilation mécanique. Déterminant incontournable, l'existence d'une dysfonction du diaphragme suscite des questionnements évidents chez les patients présentant un échec de sevrage. Pourtant, ces interrogations trouvent rarement de réponses du fait des difficultés d'analyse de la fonction diaphragmatique chez les patients de réanimation. Ceci explique que bien souvent, le diaphragme ne peut être étudié spécifiquement et qu'il est plus simple de réaliser une approche plus globale de la fonction musculaire respiratoire. La présente thèse a pour objectifs principaux d'étudier la fonction diaphragmatique en tant que déterminant du succès ou de l'échec du sevrage et de proposer des modalités d'investigations basées sur des signaux physiologiques facilement obtenus au lit des patients. Plus spécifiquement, les quatre travaux réunis dans cette thèse ont été élaborés dans la perspective de répondre à quatre principales hypothèses.

La première hypothèse est que la dysfonction diaphragmatique est très fréquente au cours du sevrage de la ventilation mécanique et qu'elle est indépendamment associée à son échec. Bien que des travaux précédents se soient déjà penchés sur cette question, aucun n'a étudié la fonction diaphragmatique avec la technique de stimulation des nerfs phréniques. Dès lors, il semble assez vraisemblable que la prévalence de la dysfonction diaphragmatique soit en réalité méconnue et vraisemblablement sous-estimée. Par ailleurs, son association avec la neuromyopathie de réanimation a été évoquée par de nombreux travaux mais n'a jamais été démontrée. L'hypothèse de ce travail est qu'il existe une dissociation entre ces deux atteintes. En effet, à l'inverse des autres muscles, le diaphragme a une activité qui ne s'interrompt jamais. En outre, il est caractérisé par une répartition en fibres musculaires qui

lui est spécifique. Il est donc logique de supposer que le repos forcé induit par la ventilation mécanique induise un processus physiopathologique différent sur le diaphragme par rapport aux conséquences de l'immobilisation prolongée sur les muscles périphériques. Compte tenu du rôle majeur du diaphragme dans le système ventilatoire, il est logique de suspecter un sévère impact pronostique de la dysfonction diaphragmatique à l'heure du sevrage.

La deuxième hypothèse est que l'échographie du diaphragme, en offrant la possibilité de mesurer l'épaississement du muscle, représente une alternative fiable à la mesure de la fonction diaphragmatique par la technique de stimulation des nerfs phréniques qui n'est disponible que dans certains centres experts. Savoir si l'échographie est une technique qui peut être utilisée de façon fiable est une question importante qui doit être évaluée. En particulier, les conditions dans lesquelles l'échographie peut être une alternative et celles qui constituent une limite à son utilisation doivent être déterminées. Là aussi, il sera intéressant d'étudier dans quelle mesure l'échographie peut se substituer à la technique de stimulation des nerfs phréniques pour analyser l'impact pronostique de la dysfonction diaphragmatique.

La troisième hypothèse est que l'estimation du couplage neuro-mécanique entre l'activité électromyographique du diaphragme et le volume courant qui en résulte pourrait également constituer une analyse intéressante de la capacité du diaphragme supporter le test de sevrage.

Enfin, *la quatrième hypothèse* dérive de la formulation de la première hypothèse. Si la fonction diaphragmatique se révèle être un déterminant majeur dans le sevrage, il serait nécessaire d'évaluer sa performance prédictive dans le succès ou l'échec du sevrage. L'hypothèse de ce travail est que la sévérité de la dysfonction diaphragmatique est un

déterminant du sevrage qui est plus important que l'existence d'une dysfonction diaphragmatique en soi.

Chapitre 1

Co-existence et impact de la dysfonction diaphragmatique et de la neuropathie de réanimation au cours du sevrage de la ventilation mécanique chez les patients de réanimation

L'imputabilité de la dysfonction diaphragmatique dans l'échec du sevrage est suggérée par plusieurs travaux. En outre, une association entre la dysfonction musculaire respiratoire, la neuromyopathie de réanimation et l'échec de sevrage est fortement suspectée. Cette relation peut paraître logique car les muscles dans leur ensemble sont l'objet d'agressions multiples au cours du séjour en réanimation. Pourtant, le diaphragme et les muscles périphériques sont différents par bien des aspects. En particulier, le diaphragme a parmi d'autres caractéristiques qui lui sont propres, celle de se contracter cycliquement de façon permanente y compris pendant le sommeil, ce qui n'est pas le cas des autres muscles. Pour cette raison, il est pertinent de supposer que le repos « forcé » du diaphragme induit par la ventilation mécanique ait des conséquences différentes que l'immobilisation allongée puisse avoir sur les autres muscles. Dans cette étude, 76 patients exposés à la ventilation mécanique pour une durée supérieure ou égale à 24 heures ont eu une évaluation de la fonction diaphragmatique par la technique de stimulation phrénique et une mesure de la force musculaire périphérique par le score MRC (Medical Research Council) le jour où ils présentaient pour la première fois les critères autorisant la réalisation d'une épreuve de ventilation spontanée. Les résultats principaux de ce travail sont les suivants : une dysfonction diaphragmatique était présente chez 48/76 patients (63%) alors qu'une neuropathie de réanimation était présente chez 26/76 (34%). Les deux atteintes étaient présentes simultanément chez 16/76 patients soit 21%. La corrélation entre la dysfonction

diaphragmatique et neuromyopathie de réanimation était significative mais faible (r = 0.26; P = 0.03). Alors que la dysfonction diaphragmatique était significativement associée à l'échec du sevrage (risque relatif 0.60; 95% intervalle de confiance : 0.45–0.79 ; P = 0.001), ce n'était pas le cas pour la neuromyopathie de réanimation. Enfin, la dysfonction diaphragmatique était significativement associée à la mortalité hospitalière et en réanimation et la neuropathie de réanimation à la durée de ventilation mécanique et de séjour en réanimation.

Cette étude démontre donc que près de deux tiers des patients entrant dans le processus de sevrage ont une dysfonction diaphragmatique et que celle-ci est indépendamment associée avec l'échec de sevrage. Ce travail montre aussi que la dysfonction diaphragmatique et la neuromyopathie de réanimation sont faiblement corrélées suggérant que ces deux entités procèdent de mécanismes physiopathologiques distincts.

Ce travail a fait l'objet d'une publication dans l'*American Journal of Respiratory and Critical Care Medicine*.

Chapitre 2

Evaluation de la fonction diaphragmatique par échographie en comparaison à la stimulation des nerfs phréniques

La technique de référence d'évaluation la fonction diaphragmatique est la mesure de la pression intra-thoracique produite par la contraction diaphragmatique en réponse à une stimulation phrénique bilatérale (Ptr,stim). Réservée aux centres experts, elle n'est pas disponible dans la plupart des services de réanimation. En revanche, l'échographie diaphragmatique est aisément disponible et a l'avantage d'être non invasive. Des données récentes montrent que l'échographie peut mesurer le degré d'épaississement (TFdi) du diaphragme et que cet indice reflèterait de façon fidèle sa fonction. D'autres données suggèrent que la mesure de l'excursion de la coupole diaphragmatique (EXdi) représenterait également un indice fiable de la fonction du diaphragme. Toutefois, le développement de cette technique comme alternative fiable à la stimulation phrénique souffre de l'absence d'une comparaison rigoureuse entre ces deux techniques. Dans ce travail, la fonction diaphragmatique de 112 patients placés sous ventilation mécanique a été analysée à deux moments prédéfinis: dans les 24 heures suivant l'intubation et après le changement de mode de ventilation marqué par le passage de la ventilation contrôlée vers l'aide inspiratoire, témoin d'une amélioration de l'état clinique. Ces deux moments étaient choisis pour permettre une comparaison de deux conditions très différentes. Lors de la première mesure, les patients sont en général suffisamment sédatés pour ne pas présenter de cycles respiratoires spontanés. A l'inverse, lors de la deuxième mesure, les patients déclenchent le ventilateur et ne sont qu'assistés par le ventilateur. Les principaux résultats de ce travail étaient les suivants : lors de la première mesure, réalisée en mode de ventilation assisté contrôlé, la Ptr,stim n'était ni corrélée avec l'épaisseur ($P = 0.28$), ni avec le TFdi ($P = 0.80$) ni

avec l'EXdi (P = 0.66). En revanche, après passage en mode d'aide inspiratoire, la relation entre Ptr,stim et TFdi était très étroite (rho=0.87, p<0.001), alors que la relation entre Ptr,stim et EXdi était modérée (rho = 0.45, p=0.001). De façon intéressante, une valeur de TFdi<29% permettait d'identifier avec une bonne performance la présence d'une dysfonction diaphragmatique définie par une Ptr,stim <11 cmH_2O (sensibilité et spécificité de 85% et 88%, respectivement). Enfin, un TFdi < 29 % était associée à une augmentation de la durée de séjour en réanimation, du temps passé sous ventilation mécanique, ainsi qu'à la mortalité.

Ce travail propose pour la première fois une validation de l'échographie diaphragmatique comme technique fiable de la mesure de la fonction diaphragmatique chez les patients de réanimation placés sous ventilation mécanique. Les implications sont importantes car ces données suggèrent que l'échographie ne peut pas être substituée à la technique de référence au cours des premières heures de ventilation mécanique lorsque les patients n'ont pas de cycles spontanés. En revanche, cette étude soutient l'hypothèse que l'échographie peut estimer la fonction diaphragmatique dès lors que les patients présentent des cycles spontanés. L'intérêt majeur de ces résultats est la possibilité d'étudier le pronostic des patients avec un outil facilement disponible dans les unités de réanimation et qui est totalement non invasif.

Ce travail a fait l'objet d'une publication dans le journal *Thorax*.

Chapitre 3

Mesure de l'activité électromyographique comme facteur prédictif du succès ou de l'échec de l'épreuve de ventilation spontanée

Le mode NAVA (Neuro-asservissement de la ventilation artificielle) est un mode de ventilation qui synchronise la délivrance des cycles avec les efforts du patient. Les efforts sont détectés au moyen d'une sonde gastrique d'alimentation équipée de huit paires d'électrodes d'électromyographie. Cette sonde permet une mesure continue de l'activité électromyographique du diaphragme (EAdi). Au cours d'une épreuve de ventilation spontanée, une telle mesure pourrait être particulièrement intéressante pour analyser le couplage entre l'EAdi et des marqueurs du profil ventilatoire.. Dans ce travail ayant inclus 57 patients présentant les critères prérequis de sevrage de la ventilation mécanique, un recueil de l'EAdi a été réalisé au cours de la première épreuve de ventilation spontanée. L'objectif était de comparer des indices descriptifs du profil ventilatoire (volume courant : V_T, fréquence respiratoire : FR, rapport FR/V_T) et à ses indices descriptifs de l'EAdi pour prédire le succès de l'épreuve de ventilation spontanée. Les patients étaient classés en échec lorsqu'ils présentaient des signes d'intolérance clinique au cours ou au terme de l'épreuve de ventilation spontanée. Au début de l'épreuve de ventilation spontanée, les grandeurs descriptives du profil ventilatoire (V_T, FR, FR/V_T) étaient similaires entre les patients réussissant le test et ceux échouant. En revanche, le pic d'activité de l'EAdi ($EAdi_{max}$) et l'aire sous la courbe inspiratoire ($EAdi_{AUC}$) étaient significativement plus bas dans le groupe succès. Au cours de l'épreuve de ventilation spontanée, le rapport FR/V_T augmentait significativement et comme attendu chez les patients du groupe échec mais l'$EAdi_{max}$ et l'$EAdi_{AUC}$ restaient stables. Il était possible de prédire le succès ou l'échec de l'épreuve de

ventilation spontanée dès la 3ème minute d'épreuve à partir des indices dérivés de l'EAdi ($EAdi_{max}$/ V_T, $EAdi_{AUC}/V_T$) avec une performance similaire au rapport FR/V_T.

Cette étude est la première à rapporter une analyse de l'EAdi au cours d'une épreuve de sevrage. Les résultats suggèrent que la mesure de l'EAdi couplée au recueil du volume courant sous la forme d'indices témoignant du couplage neuromécanique permet d'évaluer la capacité du système neuroventilatoire à assurer l'autonomie respiratoire autorisant le sevrage de la ventilation mécanique.

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

Chapitre 4

Prédiction du succès de l'épreuve de ventilation spontanée par la mesure de l'épaississement diaphragmatique et de la pression générée par la stimulation phrénique

Le travail présenté dans le chapitre 1 a montré avec la technique de référence (la stimulation des nerfs phréniques) que la dysfonction diaphragmatique, définie par une pression intrathoracique générée par la stimulation (Ptr,stim) < 11 cmH_2O, est présente chez deux tiers des patients débutant le processus de sevrage de la ventilation mécanique. Ce travail montre aussi que parmi les patients échouant le sevrage, 94% ont une dysfonction diaphragmatique mais que cette dysfonction est aussi présente chez 40% des patients réussissant le sevrage. A partir de ces données, l'hypothèse du présent travail était que le seuil de Ptr,stim définissant la dysfonction diaphragmatique (11 cmH_2O) n'était pas approprié pour prédire le succès ou l'échec du sevrage. Les patients étudiés dans l'étude du chapitre 1 ont donc fait l'objet d'une seconde analyse où ont été comparés trois marqueurs de la fonction diaphragmatique mesurés avant de débuter l'épreuve de ventilation spontanée : Ptr,stim, la fraction d'épaississement du diaphragme (TFdi) obtenue par échographie et l'indice de polypnée superficielle (RSBI). Des courbes ROC (Receiver operating characteristic) ont ensuite été construites pour déterminer la performance de chacun des trois indices pour prédire le succès du sevrage. Les seuils optimaux pour prédire le succès du sevrage étaient respectivement pour Ptr,stim, TFdi et RSBI : 7,8 cmH_2O (sensibilité 78%, spécificité 80%), 29% (sensibilité 72%, spécificité 84%) et 50 $cycles.min^{-1}.l^{-1}$ (sensibilité 66%, spécificité 68%). Les aires sous les courbes ROC de Ptr,stim et TFdi étaient similaires (0,87 and 0,85, respectivement) et significativement meilleures que celle de RSBI

(0,70). La validation de ces indices et de leur performance pour prédire le succès du sevrage a été confirmé dans une cohorte de validation.

Cette étude suggère que le seuil de Ptr,stim définissant la dysfonction diaphragmatique est plus élevé que le niveau de fonction diaphragmatique prédisant de façon optimal le succès du sevrage. L'autre résultat notable est que la mesure de l'épaississement diaphragmatique par l'échographie a une performance égale à la technique de stimulation phrénique pour prédire le succès du sevrage.

Ce travail fait l'objet d'une publication soumis à *Anesthesiology*, actuellement en cours de relecture.

Conclusions et perspectives

Ce travail de recherche en physiologie appliquée s'est intéressé à l'évaluation et à l'impact de la fonction diaphragmatique sur le succès du sevrage de la ventilation mécanique et sur le pronostic des patients en réanimation. Il s'est aussi intéressé à l'association entre la neuromyopathie de réanimation et la dysfonction diaphragmatique. Les principales conclusions et les perspectives de ce travail sont discutées ci-dessous.

Nous avons établi que la dysfonction diaphragmatique est très fréquemment présente chez des patients de réanimation au stade du sevrage de la ventilation et que cette présence est associée de façon indépendante à son échec. Parallèlement, nous avons montré que l'échographie pouvait être un substitut fiable de la technique de référence pour évaluer la fonction diaphragmatique à partir du moment où des efforts inspiratoires du patient étaient présents. En outre, les deux techniques, échographie et stimulation des nerfs phréniques, se sont avérées toutes les deux équivalentes pour prédire la survenue d'événements cliniques marquants du séjour en réanimation tels que l'échec du sevrage, la durée de séjour et de ventilation, la mortalité en réanimation et hospitalière. Nos résultats ont également montré que la mesure de l'activité électrique du diaphragme permettait d'identifier précocement au cours d'un test de ventilation spontanée les patients à risque d'échec. Ainsi, la mise en évidence d'un couplage neuro-mécanique inadapté renseigne sur la capacité d'un patient à tolérer l'exercice imposé par une épreuve de ventilation spontanée. Nos observations échographiques et celles réalisées avec le couplage neuro-mécanique diaphragmatique apportent un éclairage originale et complémentaire sur l'équilibre charge-capacité au cours du sevrage. Si nos travaux apportent des informations nouvelles sur le rôle et l'impact de la dysfonction diaphragmatique au cours du sevrage ; ils suscitent aussi de nombreuses interrogations qui justifient de poursuivre nos investigations.

En effet, si l'impact négatif d'une dysfonction diaphragmatique sur la réussite du sevrage est démontré, les déterminants de cette dysfonction ne sont pas parfaitement élucidés. En particulier, le rôle de la ventilation mécanique sur la survenue de la dysfonction diaphragmatique observée au cours du sevrage n'est pas totalement établi. En effet, une dysfonction diaphragmatique étant déjà présente dans les heures suivant l'instauration de la ventilation mécanique, il est vraisemblable que cette dysfonction initiale participe à la survenue de la dysfonction plus tardive diagnostiquée au cours du sevrage. Bien qu'il soit à ce jour difficile d'isoler l'une et l'autre de ces agressions, un effort de recherche sera nécessaire afin d'identifier leurs facteurs de risque respectifs. Ceci permettrait d'envisager une approche préventive et thérapeutique. De ce point de vue justement, beaucoup reste à faire. L'utilisation de modes ventilatoires évitant de décharger complètement la fonction diaphragmatique est intéressante mais n'est pas toujours possible notamment chez les patients présentant un syndrome de détresse respiratoire aiguë. Dans ce contexte, l'avènement d'une nouvelle technologie reposant sur la stimulation répétée (pacing) du diaphragme par voie transveineuse est séduisante. Un travail récent a montré l'efficacité de cette technologie sur la prévention de l'atrophie induite par la ventilation mécanique chez l'animal (120). La faisabilité de la technique a été établie chez des patients de réanimation (121). Ces travaux ont ouvert la voie au premier essai contrôlé (NCT03107949) visant à établir l'intérêt d'une stratégie thérapeutique reposant sur cette technologie chez des patients présentant un sevrage difficile. Notre service est actuellement engagé dans ce travail multicentrique.

La possibilité d'une amélioration de la fonction diaphragmatique au cours du sevrage reste une question non résolue. Ce travail de thèse constitue les fondements d'investigations futures cherchant à réaliser une étude répétée de la fonction

diaphragmatique depuis l'instauration de la ventilation mécanique jusqu'à l'extubation. Cela permettrait de mettre en évidence l'existence d'une réversibilité de la dysfonction initiale et le cas échéant d'en identifier ses déterminants.

Une prochaine étape devra réaliser une analyse composite de l'ensemble de la chaîne de commande et effectrice ventilatoire avec une mesure de l'activité électrique du diaphragme et simultanément une mesure échographique de l'épaississement et de son impact mécanique en terme de volume courant généré. Une telle approche permettrait une vision intégrative de la boucle commande-effectrice ventilatoire. L'unité INSERM UMRS 1158 au sein de laquelle notre équipe collabore est l'environnement idéal pour développer conjointement une telle approche translationnelle de la commande musculaire respiratoire au cours du sevrage. Un tel travail réunira des techniques d'électroencéphalographie, de mesure de l'activité électrique du diaphragme, et de son épaississement à l'échographie. Ceci permettra d'établir précisément la relation entre activité électrique du diaphragme et épaississement.

La relation entre le sevrage de la ventilation mécanique et son impact cognitif et sensoriel des patients qui y sont soumis n'a pas été encore étudiée. Notre équipe développe depuis quelques années une thématique de recherche portant sur l'analyse sensorielle et cognitive chez des sujets sains soumis à des charges respiratoires et chez des patients porteurs de handicaps respiratoires. Cette expérience acquise permettra d'étendre ces programmes de recherche aux patients de réanimation soumis au sevrage de la ventilation.

Si nous avons montré l'impact négatif de la dysfonction diaphragmatique sur le pronostic à court terme des patients de réanimation, l'impact à moyen et long terme de cette dysfonction chez les patients survivants est méconnu. Comme évoqué en amont, une première question est de savoir si cette dysfonction persiste ou si elle peut s'améliorer.

Ensuite, les conséquences en terme de pronostic fonctionnel doivent être recherchées. En effet, il est vraisemblable que les patients sortant de réanimation avec une dysfonction diaphragmatique présentent un handicap respiratoire. Hors réanimation, le diagnostic d'une dysfonction diaphragmatique survient en général au terme d'une longue histoire d'investigations de symptômes très variés (troubles du sommeil, intolérance à l'exercice, dyspnée). A l'instar des travaux réalisés avec les survivants de syndrome de détresse respiratoire aiguë présentant des séquelles fonctionnelles jusqu'à cinq ans après le séjour en réanimation ; un suivi et un dépistage des maladies potentiellement associées à la dysfonction diaphragmatique au décours d'un séjour de réanimation pourraient être justifiés. Cette hypothèse fera l'objet d'un travail de recherche clinique au sein du Service de Réadaptation Post Réanimation de notre Département. Ce travail qui débutera en fin d'année 2017 a d'ores et déjà obtenu un financement de l'Assistance Publique Hôpitaux de Paris.

Dans la continuité du projet discuté précédemment, l'association entre la dysfonction diaphragmatique et les troubles du sommeil des patients de réanimation fera l'objet d'un travail de recherche spécifique. L'étude des troubles du sommeil en réanimation est un champs d'investigation encore relativement peu exploité qui justifie d'être approfondi.

L'existence d'une dysfonction diaphragmatique est une information importante dans l'évaluation du pronostic des patients placés sous ventilation mécanique notamment à l'étape du sevrage. Nous avons montré que l'échographie semble être un outil prometteur dans la perspective de faciliter le diagnostic de la dysfonction diaphragmatique. Dans cette éventualité, il sera nécessaire de confirmer la faisabilité et la pertinence d'une mesure échographique de la fonction diaphragmatique à l'échelle multicentrique. Après cette étape, l'utilisation de l'échographie diaphragmatique pour individualiser la stratégie de prise en

charge des patients exposés à la ventilation mécanique pourra être envisagée. Ceci pourrait conduire à titrer l'assistance ventilatoire de façon à maintenir la fonction diaphragmatique dans des limites physiologiques au cours du syndrome de détresse respiratoire aiguë par exemple ou au décours de l'extubation, pour décider de l'indication d'une ventilation non invasive prophylactique.

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ORIGINAL ARTICLE

Coexistence and Impact of Limb Muscle and Diaphragm Weakness at Time of Liberation from Mechanical Ventilation in Medical Intensive Care Unit Patients

Martin Dres[1,2*], Bruno-Pierre Dubé[1,3*], Julien Mayaux[2], Julie Delemazure[2], Danielle Reuter[2], Laurent Brochard[4,5], Thomas Similowski[1,2], and Alexandre Demoule[1,2]

[1]Sorbonne Universités, UPMC University Paris 06, INSERM, UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Paris, France; [2]AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie et Réanimation Médicale (Département "R3S"), Paris, France; [3]Département de Médecine, Service de Pneumologie, Hôpital Hôtel-Dieu du Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada; [4]Keenan Research Centre for Biomedical Science of St. Michael's Hospital, Toronto, Ontario, Canada; and [5]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada

Abstract

Rationale: Intensive care unit (ICU)- and mechanical ventilation (MV)-acquired limb muscle and diaphragm dysfunction may both be associated with longer length of stay and worse outcome. Whether they are two aspects of the same entity or have a different prevalence and prognostic impact remains unclear.

Objectives: To quantify the prevalence and coexistence of these two forms of ICU-acquired weakness and their impact on outcome.

Methods: In patients undergoing a first spontaneous breathing trial after at least 24 hours of MV, diaphragm dysfunction was evaluated using twitch tracheal pressure in response to bilateral anterior magnetic phrenic nerve stimulation (a pressure <11 cm H_2O defined dysfunction) and ultrasonography (thickening fraction [TFdi] and excursion). Limb muscle weakness was defined as a Medical Research Council (MRC) score less than 48.

Measurements and Main Results: Seventy-six patients were assessed at their first spontaneous breathing trial: 63% had diaphragm dysfunction, 34% had limb muscle weakness, and 21% had both. There was a significant but weak correlation between MRC score and twitch pressure ($\rho = 0.26$; $P = 0.03$) and TFdi ($\rho = 0.28$; $P = 0.01$), respectively. Low twitch pressure (odds ratio, 0.60; 95% confidence interval, 0.45–0.79; $P < 0.001$) and TFdi (odds ratio, 0.84; 95% confidence interval, 0.76–0.92; $P < 0.001$) were independently associated with weaning failure, but the MRC score was not. Diaphragm dysfunction was associated with higher ICU and hospital mortality, and limb muscle weakness was associated with longer duration of MV and hospital stay.

Conclusions: Diaphragm dysfunction is twice as frequent as limb muscle weakness and has a direct negative impact on weaning outcome. The two types of muscle weakness have only limited overlap.

Keywords: diaphragm dysfunction; intensive care unit–acquired weakness; weaning from mechanical ventilation

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Correspondence and requests for reprints should be addressed to Martin Dres, M.D., Service de Pneumologie et Réanimation Médicale, Groupe Hospitalier Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France. E-mail: martin.dres@aphp.fr

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At a Glance Commentary

Scientific Knowledge on the Subject: Critically ill patients can develop intensive care unit–acquired weakness and intensive care unit–acquired diaphragm dysfunction. Both have been associated with poor outcome and prolonged weaning from mechanical ventilation. Whether they are two aspects of the same entity or whether they have a different prevalence and prognostic impact remains unclear. Their respective prevalence and coexistence, risk factors, and outcome at time of liberation from mechanical ventilation are not known.

What This Study Adds to the Field: At the time of liberation from mechanical ventilation, in a nonselected population, diaphragm dysfunction is twice as frequent as limb muscle weakness. Diaphragm dysfunction is significantly associated with subsequent weaning failure and mortality.

It is well established that a substantial proportion of intensive care unit (ICU) patients develop limb muscle weakness, also called ICU-acquired weakness (ICU-AW) (1, 2). In turn, ICU-AW is associated with increased duration of mechanical ventilation (MV) and ICU stay (3–7). More recently, it has been shown that mechanically ventilated ICU patients may also experience acquired diaphragm dysfunction (8, 9) and atrophy (10), which may cause difficult weaning and increased duration of MV (11–13). Although ICU-acquired limb muscle and diaphragm weaknesses are increasingly described, data regarding their interrelationship and their respective risk factors and prognostic impact are scarce and they have only been investigated in selected populations (3, 4, 13). To some extent, ICU-AW and diaphragm dysfunction share similar mechanisms and could be two aspects of the same disease in mechanically ventilated patients submitted to bed rest and general muscle disuse (8, 9, 14). However, in contrast with limb muscles, the diaphragm contracts phasically and continuously throughout the subject's lifetime. It is currently unknown whether MV has a similar impact on diaphragm and limb muscle strength.

The aim of the present study was to assess whether diaphragm dysfunction and ICU-AW are or not two distinct entities with their own specific prevalence and risk factors. In this purpose, we enrolled a nonselected population of medical ICU patients on the day of their first spontaneous breathing trial (SBT). Diaphragm function was assessed by both phrenic nerve stimulation and ultrasound, and limb muscle strength was assessed by a validated clinical tool.

The primary objective of the study was to quantify the respective prevalence of ICU-AW and diaphragm dysfunction.

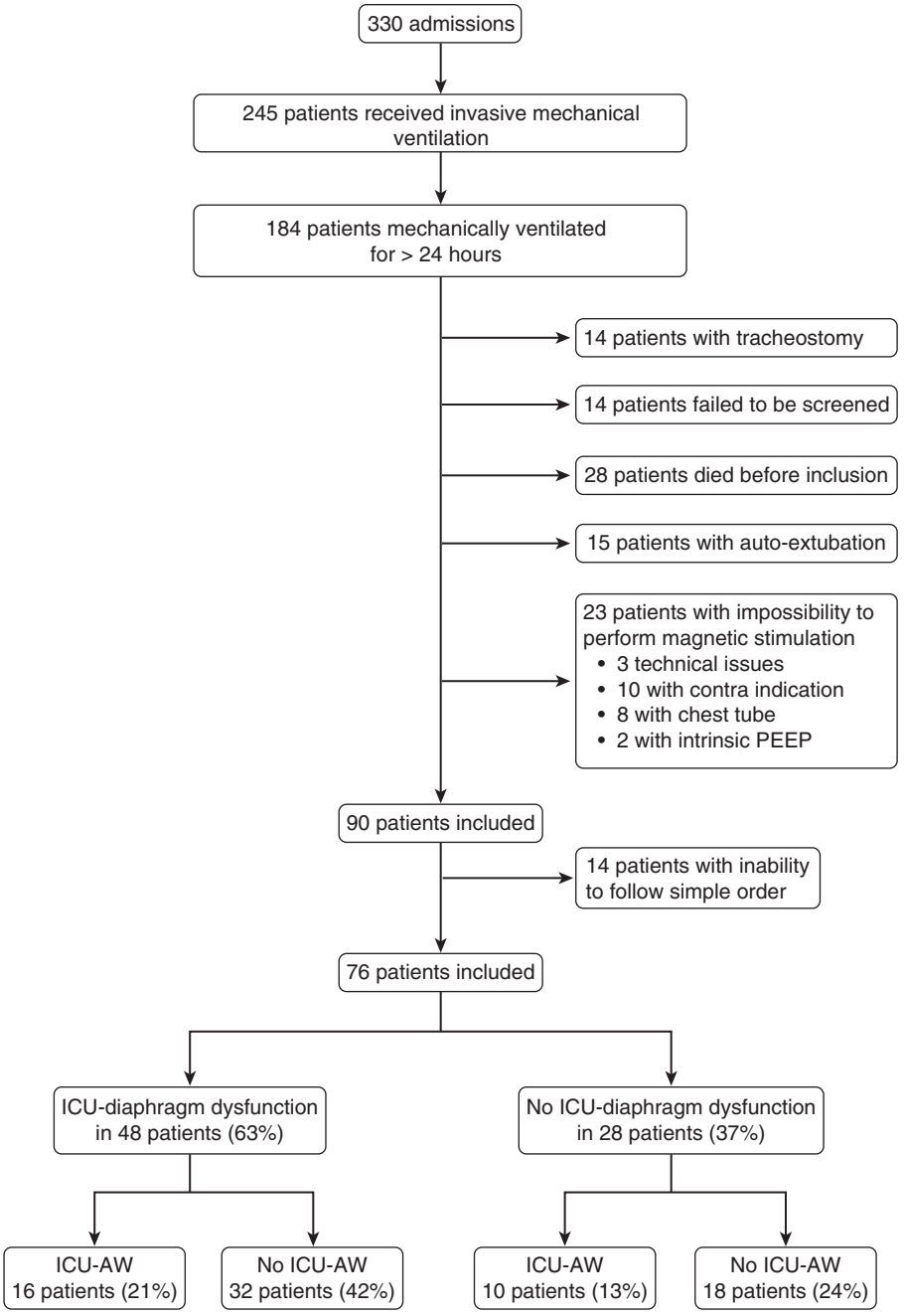

Figure 1. Study flowchart. ICU-AW = intensive care unit–acquired weakness; PEEP = positive end-expiratory pressure.

We also sought to determine the respective impact of ICU-AW and diaphragm dysfunction on weaning success and their association with clinical outcome. Some of the results of this study have been previously reported in abstract form (15).

Methods

Detailed methods are provided in the online supplement. The study was conducted over an 8-month period (December 1, 2014, to July 31, 2015) in a medical ICU. The study was approved by the Comité de Protection des Personnes Ile-de-France VI (ID RCB: 2014-A00715-42). Informed consent was obtained from all patients or their relatives.

Patients

Patients intubated and ventilated for at least 24 hours were eligible for inclusion in the study when they met the predefined readiness-to-wean criteria on daily screening (*see* online supplement) and were therefore deemed ready to undergo a first 30-minute SBT (16). Exclusion criteria were related to factors possibly interfering with tracheal pressure measurements in response to phrenic nerve stimulation (*see* online supplement), tracheostomy, and the impossibility to assess muscular strength in a limb because of immobilization or inability to follow simple orders.

Diaphragm Strength

Phrenic nerve stimulation. Diaphragm strength was assessed in terms of the changes in endotracheal tube pressure induced by bilateral phrenic nerve stimulation during airway occlusion (Ptr,stim), as described elsewhere (*see* online supplement) (17, 18). Stimulations were delivered at the maximum intensity allowed by the stimulator (100%) known to result in supramaximal diaphragm contraction in most patients (8, 18–21).

Diaphragm ultrasound measurements. Ultrasound assessment of the diaphragm was performed using a 4- to 12-MHz linear array transducer (Sparq ultrasound system; Philips Healthcare, Bothell, WA), using techniques described elsewhere (22, 23). Measurements were performed while patients were mechanically ventilated with a standardized pressure-support level targeting a tidal volume of 6–8 ml/kg of ideal body weight. Positive end-expiratory pressure was not modified during the measurements. In our unit, positive end-expiratory pressure is routinely set at around 5 cm H_2O. Diaphragm thickness was measured at end-expiration (T_{DE}) and end-inspiration (T_{DI}), and thickening fraction (TFdi) was calculated offline as $(T_{DI} - T_{DE})/T_{DE}$. The maximal excursion of the diaphragm was also measured. Ultrasound measurements were performed by one of the authors (either B.-P.D. or M.D.) on at least three separate breaths, and the mean of the three measurements was reported.

Limb Muscle Strength

Limb muscle strength was assessed by the Medical Research Council (MRC) score in patients screened for awakening and understanding (*see* online supplement). MRC scoring was performed jointly by the ICU physiotherapist and one of the investigators (B.-P.D. or M.D.).

Definitions

Ptr,stim was used to identify two groups of patients based on the 11 cm H_2O cutoff already described (8, 24). Patients with a Ptr,stim less than 11 cm H_2O were considered to have diaphragm dysfunction. MRC score was used to identify two groups of patients based on the cutoff of 48 of 60 (14). Patients with an MRC score less than 48 were considered to have ICU-AW.

Clinical Data Collection

Demographic data, comorbidities, severity scores, organ dysfunction–related variables, physiologic data, blood gas data, medication exposure, duration of MV, ICU and hospital stay, and ICU and hospital mortality were prospectively recorded.

Table 1. Patient Characteristics on Inclusion

Men, n (%)	52 (68)
Age, yr	57 ± 16
Body mass index, kg/m^2	25 ± 6
SOFA	5 ± 3
SAPS II	43 ± 2
Sepsis on admission, n (%)	42 (55)
Duration of mechanical ventilation, d	4 (2–6)
Reason for mechanical ventilation, n (%)	
Hypercapnic respiratory failure	9 (12)
Hypoxemic respiratory failure	22 (29)
Coma	22 (29)
Shock	23 (30)
Medical conditions, n (%)	
COPD	17 (22)
Cirrhosis	14 (18)
Diabetes	14 (18)
Current smoking	37 (49)
Ventilator parameters	
$F_{I_{O_2}}$, %	34 ± 5
Pressure support level, cm H_2O	10 ± 2
Tidal volume, ml/kg ideal body weight	6.9 ± 1.9
PEEP, cm H_2O	6 ± 1
Clinical parameters	
Respiratory rate, breath/min	23 ± 5
Mean arterial pressure, mm Hg	83 ± 17
Heart rate, min^{-1}	92 ± 18
Blood gases	
pH	7.43 ± 0.08
Pa_{CO_2}, mm Hg	40 ± 9
Pa_{O_2}, mm Hg	101 ± 34
$Pa_{O_2}/F_{I_{O_2}}$	292 ± 104
Lactate, mmol/L	1.6 ± 0.7

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; PEEP = positive end-expiratory pressure; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment score.
Continuous variables are expressed as mean ± SD or median (interquartile range), and categorical variables are expressed as n (%).

Study Design

The SBT was performed after completion of diaphragm and limb muscle assessment. Patients were connected to the ventilator (pressure support level 7 cm H_2O, zero end-expiratory pressure) for a 30-minute period. SBT was considered to have failed when criteria of clinical intolerance were present (*see* online supplement) (16). Otherwise, the SBT was considered to be successful and patients were extubated according to the decision of the attending physician. Patients who did not meet the predefined clinical intolerance criteria but who were not extubated after completion of the SBT were considered to be weaning failures. Successful weaning was defined as sustained spontaneous breathing without any form of ventilatory support 48 hours after extubation. Weaning failure was defined as patients failing the SBT, requiring reintubation or any form of ventilatory support (including noninvasive ventilation for postextubation acute respiratory failure, but not prophylactic noninvasive ventilation) during the 48 hours following extubation. In addition, simple, difficult, and prolonged weaning were defined according to the international weaning conference (16).

Statistical Analyses

Continuous variables are expressed as median (interquartile range) or mean (SD) and categorical variables are expressed as absolute and relative frequency. Continuous variables were compared with Student's *t* test or Mann-Whitney *U* test depending on distribution and categorical variables were compared with chi-square test or Fisher's exact test depending on sample size. The prevalence

Table 2. Patient Characteristics According to the Presence of Diaphragm Dysfunction or ICU-AW at Inclusion

	Diaphragm Dysfunction			ICU-AW		
	Yes (*n* = 48)	No (*n* = 28)	*P* Value	Yes (*n* = 26)	No (*n* = 50)	*P* Value
Demographic data						
Men, n (%)	32 (67)	20 (71)	0.67	17 (65)	35 (70)	0.68
Age, yr	61 ± 13	51 ± 18	0.01	61 ± 12	56 ± 17	0.16
Body mass index, kg/m^2	25 ± 6	26 ± 4	0.75	24 ± 3	26 ± 6	0.08
Medical conditions, n (%)						
Heart failure	10 (21)	2 (7)	0.11	3 (12)	9 (18)	0.46
COPD	10 (21)	2 (7)	0.11	2 (8)	10 (20)	0.16
Cirrhosis	8 (17)	6 (21)	0.76	9 (35)	5 (10)	0.01
Diabetes	9 (19)	5 (18)	0.92	5 (19)	9 (18)	0.90
Current smoking	25 (52)	12 (43)	0.44	12 (46)	25 (50)	0.75
On admission						
SOFA	5 ± 3	5 ± 3	0.80	6 ± 3	5 ± 3	0.04
SAPS II	46 ± 23	37 ± 21	0.09	47 ± 23	41 ± 22	0.11
Sepsis, n (%)	25 (52)	17 (61)	0.46	11 (42)	31 (62)	0.10
Reason for admission, n (%)						
Hypercapnic respiratory failure	7 (15)	2 (7)	0.47	1 (4)	8 (16)	0.15
Hypoxemic respiratory failure	17 (35)	5 (18)	0.12	10 (38)	12 (24)	0.20
Shock	17 (35)	6 (21)	0.30	9 (35)	14 (28)	0.60
Coma	7 (15)	15 (54)	0.001	6 (23)	16 (32)	0.42
Duration of MV before inclusion, d	5 (2–7)	3 (1–5)	0.04	6 (4–8)	3 (1–5)	0.01
Medication exposure before inclusion, n (%)						
Propofol	27 (57)	13 (46)	0.36	9 (35)	31 (63)	0.02
Neuromuscular blocker	9 (19)	2 (7)	0.16	3 (12)	8 (16)	0.58
Midazolam	14 (30)	11 (39)	0.40	9 (35)	16 (33)	0.86
Sufentanil	26 (55)	11 (39)	0.18	12 (46)	25 (51)	0.69
Corticosteroids	6 (13)	3 (11)	0.79	5 (19)	4 (8)	0.16
Diaphragm assessment						
Ptr,stim, cm H_2O	6.4 ± 2.4	16.5 ± 5.5	<0.001	9.3 ± 6.6	10.5 ± 6.0	0.42
T_{DE}, mm	2.11 ± 0.54	2.20 ± 0.63	0.54	2.01 (0.50)	2.21 (0.60)	0.13
Diaphragm dysfunction, %	—	—		16 (62)	32 (67)	0.83
TFdi, %	21 ± 9	40 ± 11	<0.001	26 ± 14	29 ± 13	0.40
Excursion, cm	0.94 ± 0.46	1.10 ± 0.32	0.15	0.87 ± 0.42	1.06 ± 0.40	0.11
Limb muscle assessment						
MRC score	47 ± 13	50 ± 11	0.35	34 ± 13	55 ± 4	<0.001
ICU-AW, %	16 (33)	10 (36)	0.83	—	—	
Ventilator settings at inclusion						
Pressure support level, cm H_2O	10 ± 2	10 ± 2	0.59	10 ± 3	10 ± 2	0.94
PEEP, cm H_2O	6 ± 1	6 ± 1	0.77	5 ± 1	6 ± 1	0.09
Tidal volume, ml/kg IBW	6.4 ± 1.7	7.7 ± 2.0	0.005	6.9 ± 1.9	7.0 ± 1.9	0.79

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; Excursion = maximum excursion of the diaphragm; IBW = ideal body weight; ICU-AW = intensive care unit–acquired weakness; MRC = Medical Research Council; MV = mechanical ventilation; PEEP = positive end-expiratory pressure; Ptr,stim = endotracheal tube pressure induced by bilateral phrenic nerve stimulation during airway occlusion; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment score; T_{DE} = end-expiratory diaphragm thickness; TFdi = diaphragm thickening fraction. Data are expressed as mean ± SD, median (interquartile range), or n (%).

of each category of the weaning classification (simple, difficult, and prolonged weaning) in patients with diaphragm dysfunction and ICU-AW was compared by a chi-square test. The Spearman correlation was used to test the relationship between MRC score and Ptr,stim and TFdi, respectively.

Multiple regression models were used to identify the effect of exposure pre-SBT variables on the incidence of diaphragm dysfunction, ICU-AW, and weaning failure. Finally, the associations of diaphragm dysfunction and ICU-AW on inclusion with duration of MV, length of ICU and hospital stay, and mortality were also assessed.

For all final comparisons, a P value less than or equal to 0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 21 (IBM, Chicago, IL).

Results

Study Population

During the study period, 330 patients were admitted, 184 patients were ventilated for at least 24 hours, and 76 patients were consecutively enrolled in the study (Figure 1). Patient characteristics on inclusion are detailed in Table 1. Patients had received MV for a median of 4 (2–6) days at the time of inclusion. MRC score could be obtained in all patients. At inclusion, all the patients were ventilated with a mean level of pressure support of 10 ± 2 cm H_2O and a mean level of positive end-expiratory pressure of 6 ± 1 cm H_2O.

Diaphragm and Limb Muscle Weakness

At the time of their first SBT, 48 patients (63%) had diaphragm dysfunction, 26 (34%) had ICU-AW, and 16 (21%) had both (Figure 1). Table 2 displays the patients' clinical characteristics according to the presence of diaphragm dysfunction or ICU-AW. Ptr,stim was similar in patients with and without ICU-AW (9.3 ± 6.6 vs. 10.5 ± 6.0 cm H_2O, respectively) and MRC score was similar in patients with and without diaphragm dysfunction (47 ± 13 vs. 50 ± 11, respectively). There was a significant but very weak correlation between MRC score and Ptr,stim ($\rho = 0.26$; $P = 0.03$) and between MRC score and TFdi ($\rho = 0.28$; $P = 0.01$) (Figures 2A and 2B).

Pre-SBT factors associated with diaphragm dysfunction were age and duration of MV before inclusion, whereas ICU admission for coma was inversely associated with diaphragm dysfunction (Table 2). Multivariate analysis showed that admission for coma (odds ratio [OR], 0.15; 95% confidence interval [CI], 0.05–0.44; $P = 0.001$) was inversely associated with diaphragm dysfunction (*see* Table E1 in the online supplement). Pre-SBT factors associated with ICU-AW were cirrhosis, duration of MV before inclusion, propofol exposure, and Sequential Organ Failure Assessment score at inclusion (Table 2). Multivariate analysis showed that

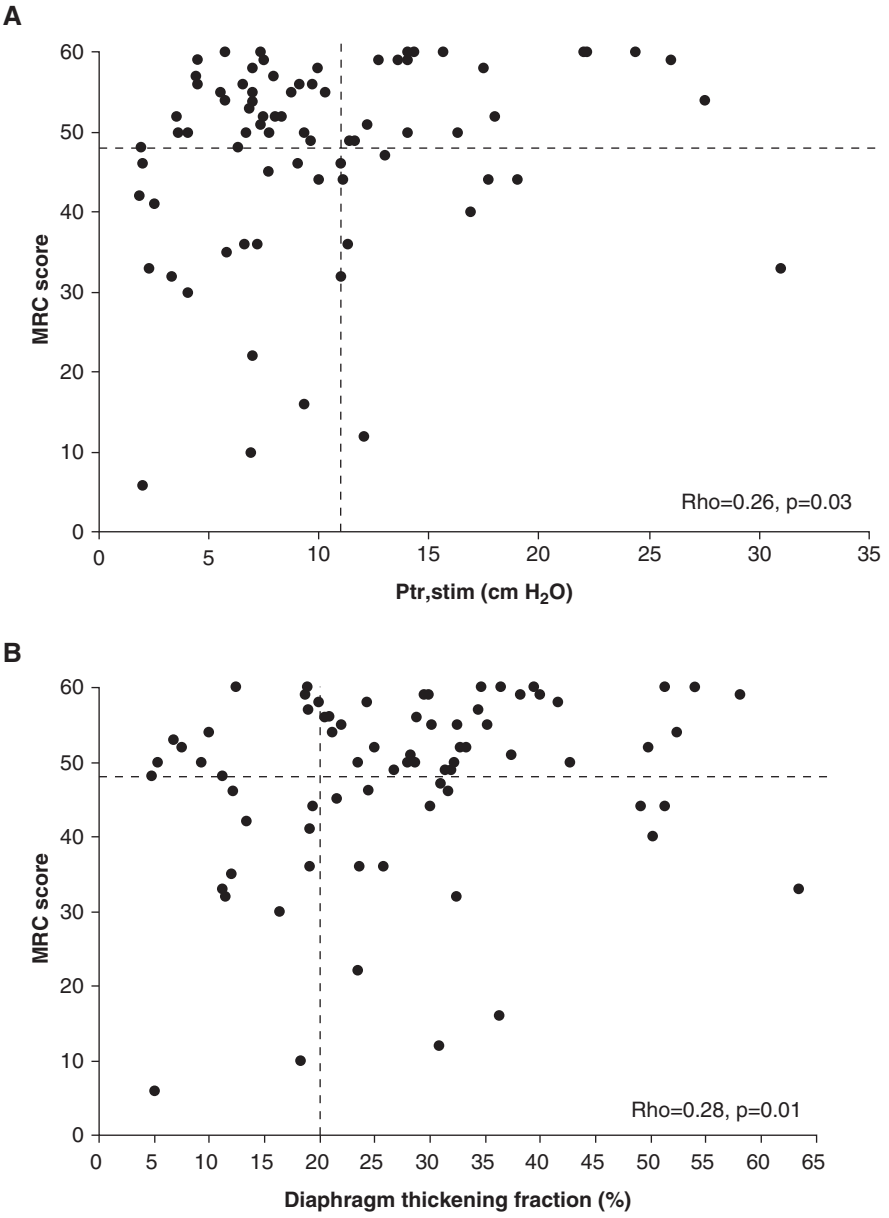

Figure 2. Correlation analysis between the Medical Research Council (MRC) score and either the change in tracheal pressure induced by bilateral phrenic nerve stimulation (Ptr,stim) (*A*) or the diaphragm thickening fraction (*B*). *Dashed lines* represent the cutoff of Ptr,stim to diagnose diaphragm dysfunction in the critically ill (−11 cm H_2O) (8), the cutoff of diaphragm thickening fraction to diagnose diaphragm dysfunction (20%) (40), and the cutoff of MRC to diagnose intensive care unit–acquired weakness (48).

longer duration of MV before inclusion (OR, 1.25; 95% CI, 1.05–1.48; $P = 0.01$) and cirrhosis (OR, 8.20; 95% CI, 1.82–37.00; $P = 0.006$) were independently associated with ICU-AW (*see* Table E2).

Weaning Outcome

Thirty-three (43%) of the 76 patients presented weaning failure. In the weaning failure group, 26 patients were not extubated at the end of the SBT, whereas the endotracheal tube was removed but ventilatory support had to be resumed within 48 hours for 7 patients. Compared with patients with successful weaning, patients with weaning failure had significantly lower MRC score, lower Ptr,stim, lower TFdi, and lower diaphragm excursion (Table 3). In addition, patients in the failure group were older, had received MV for a longer duration before inclusion, and had a higher Pa_{CO_2}. Diaphragm dysfunction was more frequent in patients with prolonged and difficult weaning than simple weaning, whereas the prevalence of ICU-AW was similar in the three categories of the weaning classification (Figure 3).

In the three logistic regression models, each including Ptr,stim, TFdi, or excursion as markers of diaphragm function, Ptr,stim (OR, 0.60; 95% CI, 0.45–0.79; $P < 0.001$), TFdi (OR, 0.84; 95% CI, 0.76–0.92; $P < 0.001$), and EXdi (OR, 0.15; 95% CI, 0.02–0.94; $P = 0.04$) were independently associated with weaning failure (Figure 4; *see* Tables E3–E5). In the model including the MRC score, the MRC score was not independently associated with weaning failure (OR, 0.96; 95% CI, 0.91–1.02; $P = 0.20$) (*see* Table E6).

Table 3. Patient Characteristics according to Weaning Outcome

	Weaning Failure (*n* = *33*; 43%)	Weaning Success (*n* = *43*; 57%)	*P* Value
Men, n (%)	23 (70)	29 (67)	0.83
Age, yr	63 ± 12	54 ± 17	0.01
Body mass index, kg/m^2	26 ± 6	25 ± 5	0.19
SOFA	5 ± 2	5 ± 3	0.77
SAPS II	46 ± 23	40 ± 21	0.23
MV before inclusion, d	6 (4–10)	3 (1–5)	<0.001
Reason for MV, n (%)			
Hypercapnic respiratory failure	6 (18)	3 (7)	0.17
Hypoxemic respiratory failure	12 (36)	10 (23)	0.31
Shock	10 (30)	13 (30)	0.99
Coma	5 (15)	17 (40)	0.02
Medical conditions, n (%)			
Chronic heart failure	4 (12)	8 (19)	0.44
COPD	8 (24)	4 (9)	0.08
Cirrhosis	9 (27)	5 (12)	0.23
Diabetes	7 (21)	7 (16)	0.77
Current smoking	17 (52)	20 (47)	0.81
Physiologic variables			
Mean arterial pressure, mm Hg	82 ± 20	84 ± 15	0.60
Heart rate, min^{-1}	95 ± 17	89 ± 18	0.15
Respiratory rate, breath/min	24 ± 5	22 ± 5	0.08
Ventilator settings			
Pressure support level, cm H_2O	10 ± 3	10 ± 2	0.36
PEEP, cm H_2O	6 ± 1	6 ± 1	0.68
Tidal volume, ml/kg IBW	6 ± 1	8 ± 2	0.001
Diaphragm activity			
TFdi, %	19 ± 9	35 ± 12	<0.001
Excursion, cm	0.82 ± 0.42	1.12 ± 0.37	0.01
T_{DE}, mm	2.20 ± 0.60	2.10 ± 0.58	0.42
Arterial blood gases			
Pa_{O_2}/Fi_{O_2}, mm Hg	256 (87)	322 (108)	0.01
Pa_{CO_2}, mm Hg	43 ± 10	37 ± 7	0.02
Diaphragm and limb function			
Ptr,stim <11 cm H_2O, n (%)	31 (94)	17 (40)	<0.001
Ptr,stim, cm H_2O	5.9 ± 2.7	13.3 ± 6.2	<0.001
Score MRC <48, n (%)	15 (46)	11 (26)	0.07
MRC score	43 ± 14	51 ± 10	0.01

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; Excursion = maximum excursion of the diaphragm; IBW = ideal body weight; MRC = Medical Research Council; MV = mechanical ventilation; PEEP = positive end-expiratory pressure; Ptr,stim = endotracheal tube pressure induced by bilateral phrenic nerve stimulation during airway occlusion; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment score; T_{DE} = end-expiratory diaphragm thickness; TFdi = diaphragm thickening fraction.
Data are expressed as mean ± SD, median (interquartile range), or n (%).

Clinical Outcome

Table 4 displays the clinical outcomes of the patients according to the presence of diaphragm dysfunction and ICU-AW on inclusion. Diaphragm dysfunction was associated with difficult weaning, prolonged weaning, prolonged total duration of MV and ICU length of stay, and higher ICU and hospital mortality. ICU-AW was associated with longer total duration of MV and hospital length of stay.

Discussion

In a nonselected population of mechanically ventilated patients deemed ready to perform a SBT, we found that the prevalence of diaphragm dysfunction was twofold higher than the prevalence of ICU-AW, with only a small overlap between diaphragm dysfunction and ICU-AW; and that diaphragm dysfunction but not ICU-AW influenced the success of weaning.

Prevalence and Correlation

This study is the first to report that the prevalence of diaphragm dysfunction at time of liberation from MV was almost twofold higher than the prevalence of ICU-AW. A recent study reported a prevalence of diaphragm dysfunction as high as 80% in patients with ICU-AW entering the weaning process (13). Interestingly, we found a similar proportion of diaphragm dysfunction in our patients with ICU-AW (16 of 26; 62%). The overall prevalence of diaphragm dysfunction observed in the present study was similar to that already described at the time of ICU admission (8). Ventilator-induced diaphragm dysfunction has been described in specific settings, such as brain-dead donors (25) and small cohorts of ICU patients (9, 26). Several factors, such as sepsis, which may be present at ICU admission and responsible for initial diaphragm weakness, might

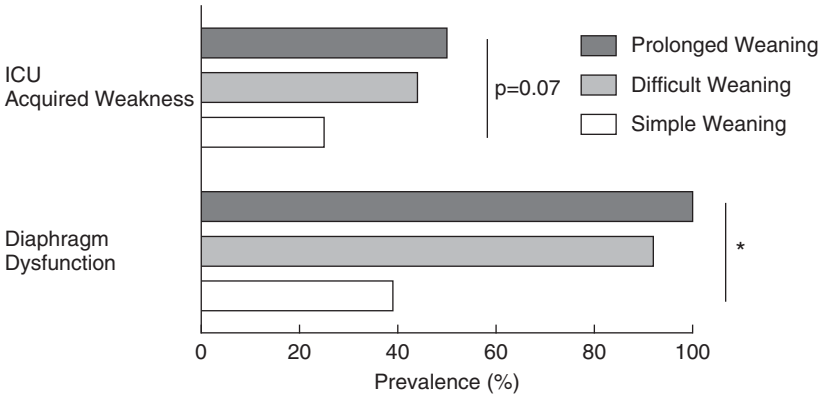

Figure 3. Histogram showing the respective prevalence of intensive care unit (ICU)-acquired weakness and diaphragm dysfunction according to the international weaning classification categories. *$P < 0.05$ (chi-square test among three groups).

improve with time, whereas other factors, such as ventilator-induced diaphragm dysfunction, may subsequently come into play. However, the respective contributions of MV and diaphragm dysfunction present on admission on the diaphragm dysfunction observed at time of weaning from MV cannot be determined from the results of this study.

The correlation between diaphragm dysfunction and ICU-AW was weak and the overlap was small. Previous studies have reported a preferential involvement of the diaphragm compared with limb muscles in patients with sepsis (27) or in mice with pneumonia (28). Ventilator-induced muscle dysfunction seems to be specific to respiratory muscles, at least the diaphragm, compared with pectoralis major for example (25). Although diaphragm and limb muscles are both skeletal muscles and share similar cellular pathway (6, 29), they seem to differ considerably in terms of their vulnerability to MV and bed rest (30). Because this was not a mechanistic study, we can only speculate on the pathophysiologic significance of our findings. However, it is essential to determine whether diaphragm dysfunction and ICU-AW are two distinct entities to address their possible mechanisms.

Immobilization is the most common of the numerous factors that may induce muscle weakness (31). Although the spontaneous activity of limb muscles may often be dramatically decreased (e.g., during sleep), the diaphragm is characterized by a continuous contractile activity throughout the subject's lifetime,

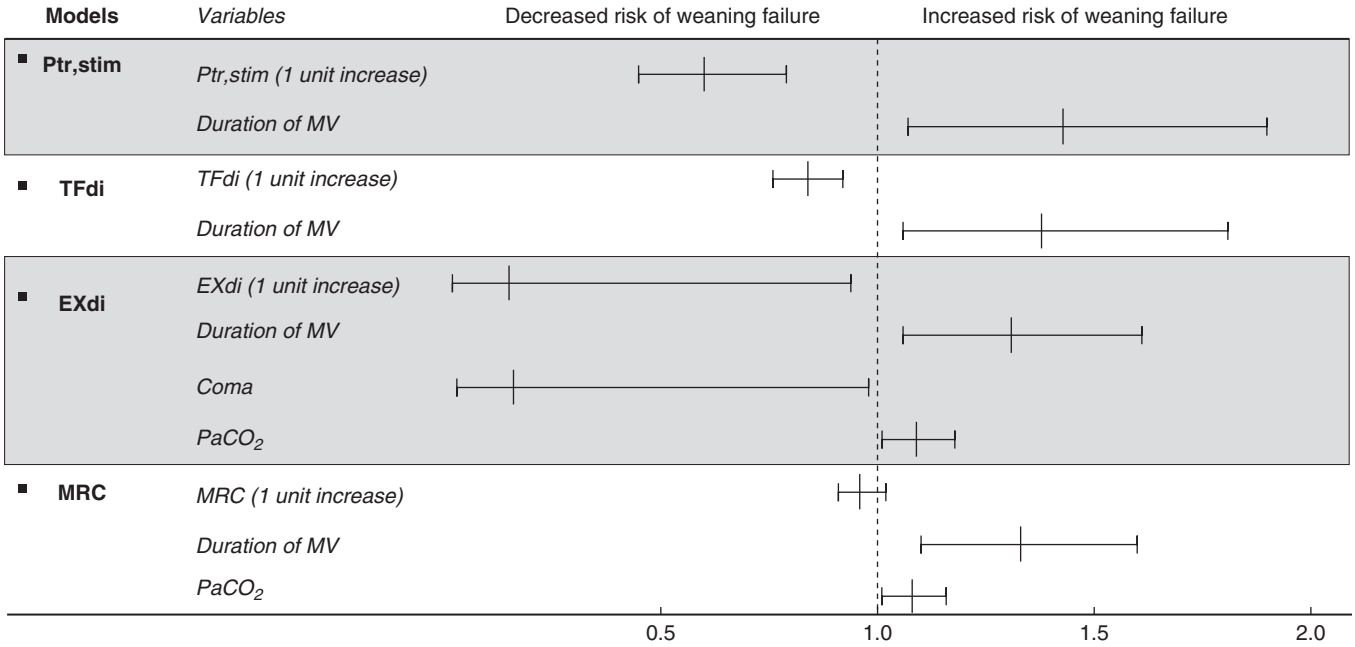

Figure 4. Forest plot showing the factors significantly associated with weaning failure: results of four multivariate logistic regressions, each separately including Ptr,stim, TFdi, EXdi, or MRC score. The Forest plot shows that an increase in the duration of mechanical ventilation before inclusion was independently associated with weaning failure in the four models. Diaphragm dysfunction was independently associated with weaning failure in the models including Ptr,stim (each 1-unit increase of Ptr,stim decreased the risk of weaning failure; odds ratio [OR], 0.60; 95% confidence interval [CI], 0.45–0.79; $P < 0.001$), TFdi (each 1-unit increase of TFdi decreased the risk of weaning failure; OR, 0.84; 95% CI, 0.76–0.92; $P < 0.001$), and EXdi (each 1-unit increase of EXdi decreased the risk of weaning failure; OR, 0.15; 95% CI, 0.02–0.94; $P = 0.04$). MRC score was not associated with weaning failure (OR, 0.96; 95% CI, 0.91–1.02; $P < 0.20$). In the model with EXdi, data were available for 58 of 76 patients. EXdi = diaphragmatic excursion; MRC = Medical Research Council score; MV = mechanical ventilation; Ptr,stim = endotracheal tube pressure induced by bilateral phrenic nerve stimulation during airway occlusion; TFdi = diaphragm thickening fraction.

Table 4. Clinical Outcome according to the Presence of Diaphragm Dysfunction and ICU-acquired Weakness

		Diaphragm Dysfunction			ICU-acquired Weakness		
	Overall Population (*n* = 76)	Yes (*n* = 48)	No (*n* = 28)	*P* Value	Yes (*n* = 26)	No (*n* = 50)	*P* Value
Difficult weaning, n (%)	25 (33)	23 (48)	2 (7)	<0.001	11 (42)	14 (28)	0.30
Prolonged weaning, n (%)	8 (10)	8 (17)	0 (0)	0.02	4 (15)	4 (8)	0.43
Total duration of MV, d	5 (2–10)	7 (4–12)	4 (1–6)	0.04	7 (4–12)	5 (1–7)	0.04
Length of ICU stay, d	8 (4–15)	10 (5–16)	6 (3–10)	0.05	9 (6–17)	6 (3–14)	0.17
Length of hospital stay, d	21 (9–30)	23 (15–32)	18 (6–29)	0.09	26 (14–37)	19 (8–28)	0.008
ICU mortality, n (%)	8 (10)	8 (17)	0 (0)	0.02	5 (19)	3 (6)	0.11
Hospital mortality, n (%)	12 (16)	11 (23)	1 (4)	0.04	7 (27)	5 (10)	0.09

Definition of abbreviations: ICU = intensive care unit; MV = mechanical ventilation.
Data are expressed as median (interquartile range) or n (%).

which could explain why the diaphragm is more susceptible to even brief periods of inactivity. This hypothesis is only speculative, but our overall findings suggest that ICU-AW and diaphragm dysfunction are two distinct syndromes probably associated with different pathophysiologic pathways.

Impact of Diaphragm Dysfunction and ICU-AW on Weaning Failure

Diaphragm dysfunction was significantly associated with subsequent difficult and prolonged weaning, but ICU-AW was not, confirming the results of previous studies assessing diaphragm dysfunction with phrenic nerve stimulation or ultrasound (11–13). As also reported by Kim and colleagues (11), we found that the maximum excursion of the diaphragm was significantly different according to the outcome of the SBT. Moreover, we also report, for the first time, that TFdi was an independent variable of weaning failure in addition to Ptr,stim. Although ultrasound measurements were performed under pressure support, it was interesting to observe a marked difference in TFdi (21 ± 9% vs. 40 ± 11%) between patients with or without diaphragm dysfunction under a similar level of pressure support ventilation (10 ± 2 vs. 10 ± 2 cm H_2O). This finding suggests that, despite the same level of support, there was a much lower contribution of the diaphragm in patients with diaphragm dysfunction than in patients without diaphragm dysfunction, as reflected by lower tidal volumes in patients with diaphragm dysfunction.

Although some patients with diaphragm dysfunction can be easily extubated, diaphragm dysfunction was present in almost all patients with weaning failure. In contrast, ICU-AW was not associated with weaning failure, but with a longer duration of MV. These findings could be explained by the small number of cases of ICU-AW diagnosed in our population. However, it is noteworthy that our patients were assessed after a relatively short period of MV compared with other studies focusing on ICU-AW that selected patients who had been ventilated for at least 7 days (3, 4, 32). MV is most often associated with bed rest, which may lead to peripheral muscle inactivity and therefore ICU-AW. Whether prolonged duration of MV, by promoting bed rest, leads to ICU-AW (33) or whether ICU-AW induces prolonged duration of MV remains unclear.

Strengths and Weakness

A major strength of our study is the inclusion of unselected mechanically ventilated ICU patients; we did not restrict inclusion to patients with severe ICU-AW or prolonged MV. Our cohort is therefore more likely to reflect the patients encountered in routine ICU practice. Another strength of our study is that we measured diaphragm function by magnetic stimulation of the phrenic nerve, which constitutes the gold standard but which is a fairly difficult technique, and ultrasound, which is easier to use in everyday practice.

Several limitations must be acknowledged. First, by using phrenic nerve stimulation as the reference technique to define diaphragm dysfunction (8, 13, 18), we excluded some eligible patients, in whom this technique was contraindicated. The cutoff of 11 cm H_2O of Ptr,stim to define diaphragm dysfunction has been recommended in ICU patients (17, 24) and validated in this population by a previous study from our group (8). Because the supramaximal nature of phrenic nerve stimulation in terms of diaphragm contraction was not specifically confirmed, we therefore cannot absolutely rule out that incomplete recruitment of phrenic nerve fibers may have contributed to low twitch pressure in some cases. However, phrenic nerve stimulation was delivered at the maximum available intensity (100% of the output of paired 2.5-T biphasic stimulators), an intensity known to result in supramaximal stimulation in most patients (8, 18–21).

Second, we defined weaning failure in the presence of clinical intolerance or by the need for any ventilator support during the 48 hours after extubation. However, among the 43 successful patients, only one was reintubated between 48 hours and Day 7 after extubation. This patient had a Ptr,stim value of 17 cm H_2O. We consequently consider that extending the duration of extubation failure in our population would not have changed our findings. In fact, weaning failure may not necessarily be directly induced by diaphragm dysfunction or ICU-AW, because several other causes could impair the weaning process (34, 35). Third, ICU-AW was determined using the MRC score and not with a dynamometer, such as the measure of the adductor pollicis muscle function by magnetic stimulation of the ulnar nerve (36). We found that MRC was validated in ICU patients by much more studies than dynamometer and was also less time consuming and technically demanding. Lastly, for obvious technical reasons, this was a single-center study in a medical ICU with a limited number of patients, which may limit the generalizability of our findings concerning

the prevalence of diaphragm dysfunction in other settings.

Conclusions

In patients undergoing their first SBT, we report a high prevalence of diaphragm dysfunction, which was associated with a higher rate of weaning failure and mortality. In contrast, the prevalence of ICU-AW was lower and not strongly correlated with diaphragm dysfunction, but was associated with a longer duration of MV and a longer ICU stay. Because the respective risk factors of ICU-AW and diaphragm dysfunction were also different, our findings raise the hypothesis that the respective potential contributors of ICU-acquired muscle weakness may have different consequences on the diaphragm and peripheral muscles with respect to the length of ICU stay. The association between diaphragm dysfunction and weaning failure demonstrated by our study fuels the notion that diaphragm dysfunction should be the object of prevention and possibly specific interventions (37–39). This should be the target of specific research studies. ■

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

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Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical ICU patients

Martin Dres, MD, Bruno-Pierre Dubé, MD, Julien Mayaux MD, Julie Delemazure, MD, Danielle Reuter, Laurent Brochard, MD, PhD, Thomas Similowski, MD, PhD; Alexandre Demoule, MD, PhD

Online supplement

Methods

Patients

Patients were eligible for inclusion in the study when they fulfilled the readiness criteria to start a spontaneous breathing trial (SBT) (1). Those criteria were: (1) adequate oxygenation as stated by a SpO2 >90% on a fraction of inspired oxygen (FiO2) ≤40% and positive end expiratory pressure (PEEP) ≤8 cmH_2O, (2) adequate pulmonary function as stated by a respiratory rate ≤35/min, (3) a cooperative cognitive state, (4) stable cardiovascular status as stated by a systolic arterial blood pressure of 90-160 mmHg without or minimal vasopressors and heart rate ≤140/min. Exclusion criteria were: inability to follow simple order enabling to perform MRC score and contraindications or impossibility to perform magnetic stimulation of the phrenic nerves (cardiac pacemaker or implanted defibrillator, cervical implants), use of neuromuscular blocking agents within the 24 hours preceding the first diaphragm function assessment (with the

exception of succinylcholine used during rapid-sequence induction of anaesthesia for intubation), pre-existing neuromuscular disorders, factors possibly interfering with tracheal pressure measurements in response to phrenic stimulation (multiple functioning chest drains, intrinsic positive end expiratory pressure). Finally, age less than 18 years, known pregnancy, and a decision to withhold life-sustaining treatment were also exclusion criteria.

Protocol

Spontaneous breathing trial protocol

When the patients fulfilled the readiness-to-wean criteria, a 30-min SBT was performed with the patient connected to the ventilator (pressure support level 7 cmH_2O, zero end expiratory pressure). The SBT was considered to be a failure if at least one the following criteria was present: (1) blood oxygen saturation (SpO_2) of < 90 % with a fraction of inspired oxygen (FiO_2) ≥ 50 %; (2) acute respiratory distress (RR ≥ 40/min, agitation, cyanosis); (3) systolic arterial blood pressure of ≥ 180 mmHg; (4) cardiac arrhythmias; (5) respiratory acidosis [pH<7.32 with an arterial carbon dioxide tension ($PaCO_2$) of ≥ 50 mmHg]. If none of these failure criteria was present, the SBT was considered as successfully completed and the patient was extubated. The decision was taken by the attending physician. If the patient did not meet the predefined clinical intolerance criteria but was not extubated after completion of the SBT, he was considered as a weaning failure. The patient was reconnected if signs of intolerance (see above) were present. The separation from the ventilator and the endotracheal tube was considered as a success (weaning success) when spontaneous breathing could be sustained without any form of ventilatory support until 48h after extubation. Conversely, cases of failure

included patients who failed the SBT and patients requiring reintubation or any form of ventilator support (including non-invasive ventilation for post-extubation acute respiratory failure) during the first 48h after extubation (weaning failure). Patients were only studied once, at the first SBT.

Assessment of the diaphragm pressure generating capacity with the phrenic nerves stimulation

Diaphragm pressure generating capacity was assessed in terms of the changes in endotracheal tube pressure induced by bilateral phrenic nerve stimulation during airway occlusion (Ptr,stim) (2–4). Phrenic nerve stimulation was performed by bilateral anterior magnetic stimulation. Briefly, two figure-of-eight coils connected to a pair of Magstim® 200 stimulators (The Magstim Company, Dyfed, UK) were positioned immediately posterior to the sternomastoid muscles at the level of the cricoid cartilage. Stimulations were delivered at the maximum output intensity of the stimulator (100%) that is known to consistently result in supramaximal phrenic contraction (3, 5–7). The patients were studied in a standardized semi-recumbent position, as follows: end-expiratory pressure was set to zero and the patient was allowed to exhale during an end-expiratory pause. Intrinsic positive end expiratory pressure was found when at relaxed end-expiration, the endotracheal pressure could not reach the zero baseline while the endotracheal tube was disconnected from the ventilator, manually occluded and by checking the absence of respiratory effort. While the endotracheal tube was manually occluded, bilateral anterolateral magnetic stimulation was performed. The absence of active respiratory efforts in response to stimulation was determined by checking the stability of the airway pressure signal. Two operators were required to achieve both stimulation and

measurements. After determining the optimal position of the coils, at least three stimulations were performed at 100% of maximal output allowed by the stimulator. Stimulations were separated by at least 60-sec to avoid superposition. The average of the three measures was taken into account for analysis. Ptr,stim was defined as the amplitude of the negative pressure wave following stimulation, taken from baseline to peak. It was measured at the proximal external end of the endotracheal tube, using a linear differential pressure transducer (MP45 ±100 cmH2O, Validyne, Northridge, Calif., USA). The pressure signal was sampled and digitized at 128 Hz (MP30, Biopac Systems, Santa Barbara, Calif., USA or Powerlab, AD Instruments, Bella Vista, Australia) for subsequent data analysis.

Assessment of diaphragmatic thickening with ultrasound

Ultrasound measurements were performed by two investigators after a 2 months training session in diaphragmatic ultrasound. Inter-observer reliability of the ultrasound measurements was assessed using intra-class correlation (ICC) on a sample of the first 20 patients enrolled in the study while the two observers were blinded to each other's measurements. ICC for the measurements of end-expiratory diaphragm thickness (T_{DE}) and end-inspiratory diaphragm thickness (T_{DI}) were measured using electronic calipers. ICC for T_{DI}, T_{DE} and diaphragm thickening fraction (TFdi) were respectively: ICC=0.95 ($p<0.001$), ICC=0.96 ($p<0.001$) and ICC=0.87 ($p<0.001$).

Ultrasound assessment of the diaphragm thickening was performed using a 4-12 MHz linear array transducer (Sparq ultrasound system, Phillips, Philips Healthcare, Andover, MA, USA). As previously reported (8, 9), the probe was placed perpendicular to the right chest wall, at the midaxillary line between the 9th and 10th right intercostal

spaces (at the level of the zone of apposition) and the right diaphragm was identified as a three-layered structure comprising two hyperechoic lines representing the pleural and peritoneal membranes and an middle hypoechoic layer representing the diaphragmatic muscle fibers. Using M-mode at a sweep speed of 10 mm/s, at least three spontaneous quiet breathing cycles were recorded and the image was frozen. Diaphragm thickness was measured at end-expiration (T_{DE}) and end-inspiration (T_{DI}) using electronic calipers. The thickening fraction of the diaphragm (TFdi) was calculated offline as $(T_{DI} - T_{DE})/ T_{DE}$.

Diaphragm excursion was measured using a 2-6 Mhz broadband curved array transducer, with the same ultrasound machine. The probe was placed below the right costal margin and directed medially and cephalad. The diaphragm was identified as the hyperechoic linear structure cephalad to the liver, and its excursion measured using M-mode.

For all measurement, at least three valid breathing cycles were recorded, and the average of the individual values was reported. Ultrasounds were performed by one of the investigators (either B.P.D or M.D.).

Study Protocol

Just before to start the SBT, we analysed the diaphragm and limbs muscles strength during 3 steps in a random basis. During the first step, we recorded Ptr,stim with the phrenic nerves stimulation technic while the patient was briefly disconnected from the ventilator in order to measure the changes in endotracheal tube pressure induced by bilateral phrenic nerve stimulation during airway occlusion. During the second step, we measured with diaphragm ultrasound, end inspiratory and expiratory diaphragm thickness

and maximal diaphragm excursion. During the third step, we evaluated the limbs muscles strength with the Medical Research Council score. During the second and the third step, patients were ventilated under pressure support with a level of assistance set to target a tidal volume of 6 to 8 ml/kg of ideal body weight. PEEP was not modified during the measurements. In our unit, PEEP is routinely set at around 5 cmH_2O.

Clinical data collection

Demographic data, severity scores, organ dysfunction–related variables, physiological data, blood gas data, presence of sepsis (10) and medications were recorded. The durations of mechanical ventilation, ICU stay and hospital stay, ICU and hospital mortality were also recorded. The ICU mortality was censored at 60 days and hospital mortality at 90 days. We also defined difficult and prolonged weaning according the International Weaning Conference (1). Difficult weaning included patients who required up to three SBT or as long as 7 days from the first SBT to achieve successful weaning and prolonged weaning, includes patients who require more than three SBT or 7 days of weaning after the first SBT (1).

Statistical analysis

Potential risk factors for the presence of diaphragm dysfunction, ICU-AW and weaning failure were assessed with univariate analysis using only factors present before the SBT. Then, logistic regression models were built for each occurrence (diaphragm dysfunction, ICU-AW and weaning failure) as follows:

Impact of exposure variables on the occurrence of ICU-AW

To assess the impact of exposure variables on the occurrence of ICU-AW, forward logistic regression models were built. The dependent variable was the occurrence of ICU-

AW at time of liberation from mechanical ventilation (the day of the first SBT). Due to the number of events in the cohort, the number of exposure variables entering into the model was limited (11). Only the variables with a p value below 0.05 were selected.

Impact of exposure variables on the occurrence of diaphragm dysfunction

To assess the impact of exposure variables on the occurrence of diaphragm dysfunction, forward logistic regression models were built. The dependent variable was the occurrence of diaphragm dysfunction at time of liberation from mechanical ventilation (the day of the first SBT). Due to the number of events in the cohort, the number of exposure variables entering into the model was limited (11). Only the variables with a p value below 0.05 were selected.

Impact of diaphragm dysfunction and ICU-AW on weaning failure

The impact of diaphragm and limb muscle strength on subsequent weaning outcome was further assessed. Each potential risk factor for weaning failure was evaluated in a univariate model. Then, four separated forward logistic regressions were performed. Ptr,stim, TFdi, excursion and MRC score, as continuous variables, were each entered into separate multivariate analyses of weaning failure, along with other variables with a p value of <0.05 in univariate analysis.

Finally, the associations of diaphragm dysfunction and ICU-AW at inclusion with duration of MV, ICU and hospital length of stay and mortality were further assessed.

Sample size calculation

After the first 20 patients studied, we observed a prevalence of 60% of diaphragm dysfunction and 30% of weaning failure. We reasoned that a sample size of 68 was necessary to allow the identification of an absolute difference of 20% in the proportion of

weaning failure in patients with diaphragm dysfunction compared to those without, with a power of 80% and α=0.05. Due to possible loss of follow-up we enrolled 10% more patients. For all final comparisons, a p-value less than or equal to 0.05 was considered statistically significant. Analyses were performed using SPSS, v.21 (IBM, Chicago, Illinois, USA).

Results

Table E1. Impact of exposure variables on the occurrence of diaphragm dysfunction

Variables	Event	Univariate analysis		Multivariate analysis			
			P value	B	OR	95% CI	P value
Age, *years*	Diaphragm Dysfunction	61±13	0.01	0.022	1.02	0.99 – 1.06	0.24
	No Diaphragm Dysfunction	51±18					
Coma[1], *n (%)*	Diaphragm Dysfunction	7 (15)	0.001	-1.911	0.15	0.05 – 0.44	0.001
	No Diaphragm Dysfunction	15 (54)					
Days of MV[2], *days*	Diaphragm dysfunction	5 (2-7)	0.04	0.072	1.07	0.91 – 1.27	0.41
	No Diaphragm Dysfunction	3 (1-5)					

MV, Mechanical ventilation; OR, Odd ratio; CI, Confidence interval, B, Intercept.
[1]Main reason for intubation, [2]Prior inclusion

Table E2. Impact of exposure variables on the occurrence of ICU-AW

Variables	Event	Univariate analysis		Multivariate analysis			
			P value	B	OR	95% CI	P value
Cirrhosis, *n (%)*	ICU-AW	9/26	0.01	2.104	8.20	1.82 – 37.00	0.006
	No ICU-AW	5/50					
SOFA score[1]	ICU-AW	6±3	0.04	0.008	1.01	0.82 – 1.24	0.94
	No ICU-AW	5±3					
Days of MV[2], *days*	ICU-AW	6 (4-8)	0.01	0.219	1.25	1.05 – 1.48	0.01
	No ICU-AW	3 (1-5)					
Propofol[3], *n (%)*	ICU-AW	9/26	0.02	-0.738	0.48	0.15 – 1.50	0.21
	No ICU-AW	31/50					

SOFA, Sequential organ failure assessment; MV, Mechanical ventilation; ICU-AW, Intensive care unit – acquired weakness; OR, Odd ratio; CI, Confidence interval, B, Intercept.
[1]On admission, [2]Prior inclusion, [3]Exposure prior inclusion.

Table E3. Impact exposure variables on weaning failure (with Ptr,stim)

Variables	Event	Univariate analysis		Multivariate analysis			
			P value	B	OR	95% CI	P value
Ptr,stim, *cmH_2O*	Weaning Failure	5.9±2.7	<0.001	-0.511	0.60	0.45 – 0.79	<0.001
	No Weaning Failure	13.3±6.2					
Age, *years*	Weaning Failure	63±12	0.01	-0.015	0.99	0.94– 1.04	0.58
	No Weaning Failure	54±17					
Days of MV[1], *days*	Weaning Failure	6 (4-10)	<0.001	0.356	1.43	1.07 – 1.90	0.02
	No Weaning Failure	3 (1-5)					
Coma[2], *n (%)*	Weaning Failure	5 (15)	0.02	-1.014	0.36	0.06 – 2.31	0.28
	No Weaning Failure	17 (40)					
PaO_2/FiO_2 ratio[1]	Weaning Failure	256 (87)	0.01	0.001	1.00	0.99 – 1.01	0.92
	No Weaning Failure	322 (108)					
$PaCO_2$[1], *mmHg*	Weaning Failure	43±10	0.02	0.052	1.05	0.95 – 1.16	0.31
	No Weaning Failure	37±7					

Ptr,stim, Endotracheal tube pressure induced by bilateral phrenic nerve stimulation during airway occlusion; MV, Mechanical ventilation; PaO_2/FiO_2, ratio of arterial oxygen tension to inspired oxygen fraction; $PaCO_2$, Partial carbon dioxide tension; OR, Odd ratio; CI, Confidence interval, B, Intercept.
[1]Prior inclusion, [2]Main reason for intubation.

Table E4. Impact exposure variables on weaning failure (with TFdi)

Variables	Event	Univariate analysis		Multivariate analysis			
			P value	B	OR	95% CI	P value
TFdi, *%*	Weaning Failure	19±9	<0.001	-0.177	0.84	0.76 – 0.92	<0.001
	No Weaning Failure	35±12					
Age, *years*	Weaning Failure	63±12	0.01	-0.013	1.01	0.96– 1.07	0.62
	No Weaning Failure	54±17					
Days of MV[1], *days*	Weaning Failure	6 (4-10)	<0.001	0.325	1.38	1.06 – 1.81	0.02
	No Weaning Failure	3 (1-5)					
Coma[2], *n (%)*	Weaning Failure	5 (15)	0.02	-1.268	0.28	0.05 – 1.58	0.15
	No Weaning Failure	17 (40)					
PaO_2/FiO_2 ratio[1]	Weaning Failure	256 (87)	0.01	-0.002	0.99	0.99 – 1.00	0.73
	No Weaning Failure	322 (108)					
$PaCO_2$[1], *mmHg*	Weaning Failure	43±10	0.02	0.034	1.04	0.95 – 1.13	0.46
	No Weaning Failure	37±7					

TFdi, Diaphragm thickening fraction; MV, Mechanical ventilation; PaO_2/FiO_2, ratio of arterial oxygen tension to inspired oxygen fraction; $PaCO_2$, Partial carbon dioxide tension; OR, Odd ratio; CI, Confidence interval, B, Intercept.
[1]Prior inclusion, [2]Main reason for intubation.

Table E5. Impact exposure variables on weaning failure (with Diaphragm excursion)

Variables	Event	Univariate analysis		Multivariate analysis			
			P value	B	OR	95% CI	P value
EXdi[#], *cm*	Weaning Failure	0.82±0.42	0.01	-1.894	0.15	0.02 – 0.94	0.04
	No Weaning Failure	1.12±0.37					
Age, *years*	Weaning Failure	63±12	0.01	-0.017	0.98	0.93 – 1.04	0.54
	No Weaning Failure	54±17					
Days of MV[1], *days*	Weaning Failure	6 (4-10)	<0.001	0.271	1.31	1.06 – 1.61	0.01
	No Weaning Failure	3 (1-5)					
Coma[2], *n (%)*	Weaning Failure	5 (15)	0.02	-1.81	0.16	0.03 – 0.98	0.05
	No Weaning Failure	17 (40)					
PaO_2/FiO_2 ratio[1]	Weaning Failure	256 (87)	0.01	-0.001	0.99	0.99 – 1.01	0.74
	No Weaning Failure	322 (108)					
$PaCO_2$[1], *mmHg*	Weaning Failure	43±10	0.02	0.082	1.09	1.01 – 1.18	0.04
	No Weaning Failure	37±7					

EXdi, Excursion of diaphragm; MV, Mechanical ventilation; PaO_2/FiO_2, ratio of arterial oxygen tension to inspired oxygen fraction; $PaCO_2$, Partial carbon dioxide tension; OR, Odd ratio; CI, Confidence interval, B, Intercept.
[1]Prior inclusion, [2]Main reason for intubation.
[#]Data available for 58/76 patients.

Table E6. Impact exposure variables on weaning failure (with MRC)

Variables	Event	Univariate analysis		Multivariate analysis			
			P value	B	OR	95% CI	P value
MRC score, *point*	Weaning Failure	43±14	0.01	-0.037	0.96	0.91 – 1.02	0.20
	No Weaning Failure	51±10					
Age, *years*	Weaning Failure	63±12	0.01	0.006	1.01	0.96 – 1.05	0.79
	No Weaning Failure	54±17					
Days of MV[1], *days*	Weaning Failure	6 (4-10)	<0.001	0.283	1.33	1.10 – 1.60	0.003
	No Weaning Failure	3 (1-5)					
Coma[2], *n (%)*	Weaning Failure	5 (15)	0.02	-0.741	0.48	0.12 – 1.95	0.30
	No Weaning Failure	17 (40)					
PaO_2/FiO_2 ratio	Weaning Failure	256 (87)	0.01	0.077	1.00	0.99 – 1.01	0.42
	No Weaning Failure	322 (108)					
$PaCO_2$, *mmHg*	Weaning Failure	43±10	0.02	0.079	1.08	1.01 – 1.16	0.02
	No Weaning Failure	37±7					

MRC, Medical research council score; MV, Mechanical ventilation; PaO_2/FiO_2, ratio of arterial oxygen tension to inspired oxygen fraction; $PaCO_2$, Partial carbon dioxide tension; OR, Odd ratio; CI, Confidence interval, B, Intercept.
[1]Prior inclusion, [2]Main reason for intubation.

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ORIGINAL ARTICLE

Ultrasound evaluation of diaphragm function in mechanically ventilated patients: comparison to phrenic stimulation and prognostic implications

Bruno-Pierre Dubé,[1,2] Martin Dres,[1,3] Julien Mayaux,[3] Suela Demiri,[3] Thomas Similowski,[1,3] Alexandre Demoule[1,3]

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[1]Sorbonne Universités, UPMC Univ Paris 06, INSERM, UMRS1158 Neurophysiologie respiratoire expérimentale et clinique, Paris, France
[2]Département de médecine, service de pneumologie, Hôpital Hôtel-Dieu du Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, Québec, Canada
[3]AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie et Réanimation Médicale (Département "R3S"), F-75013, Paris, France

Correspondence to
Dr Alexandre Demoule, Service de Pneumologie et Réanimation Médicale, Groupe Hospitalier Pitié-Salpêtrière, 47-83 boulevard de l'Hôpital, 75651 Paris Cedex 13, France; alexandre.demoule@aphp.fr

B-PD and MD contributed equally

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ABSTRACT

Rationale In intensive care unit (ICU) patients, diaphragm dysfunction is associated with adverse clinical outcomes. Ultrasound measurements of diaphragm thickness, excursion (EXdi) and thickening fraction (TFdi) are putative estimators of diaphragm function, but have never been compared with phrenic nerve stimulation. Our aim was to describe the relationship between these variables and diaphragm function evaluated using the change in endotracheal pressure after phrenic nerve stimulation (Ptr,stim), and to compare their prognostic value.

Methods Between November 2014 and June 2015, Ptr,stim and ultrasound variables were measured in mechanically ventilated patients <24 hours after intubation ('initiation of mechanical ventilation (MV)', under assist-control ventilation, ACV) and at the time of switch to pressure support ventilation ('switch to PSV'), and compared using Spearman's correlation and receiver operating characteristic curve analysis. Diaphragm dysfunction was defined as Ptr,stim <11 cm H_2O.

Results 112 patients were included. At initiation of MV, Ptr,stim was not correlated to diaphragm thickness (p=0.28), EXdi (p=0.66) or TFdi (p=0.80). At switch to PSV, TFdi and EXdi were respectively very strongly and moderately correlated to Ptr,stim, (r=0.87, p<0.001 and 0.45, p=0.001), but diaphragm thickness was not (p=0.45). A TFdi <29% could reliably identify diaphragm dysfunction (sensitivity and specificity of 85% and 88%), but diaphragm thickness and EXdi could not. This value was associated with increased duration of ICU stay and MV, and mortality.

Conclusions Under ACV, diaphragm thickness, EXdi and TFdi were uncorrelated to Ptr,stim. Under PSV, TFdi was strongly correlated to diaphragm strength and both were predictors of remaining length of MV and ICU and hospital death.

Key messages

What is the key question?

- In critically ill patients undergoing mechanical ventilation (MV), are ultrasound diaphragm measurements reliable estimators of diaphragm function as assessed with the gold standard phrenic stimulation technique (Ptr,stim) and are they associated with clinical outcomes?

What is the bottom line?

- Neither diaphragm thickness, its excursion or its thickening fraction (TFdi) were correlated to diaphragm function at the moment of initiation of MV, but TFdi alone was strongly correlated to Ptr,stim and to clinical outcome at the moment of switch to pressure support ventilation.

Why read on?

- This study is the first to systematically compare various ultrasonographic markers of diaphragm function to phrenic nerve stimulation in MV patients, providing a better understanding of the conditions in which these markers can act as reliable estimators of diaphragm function and clinical outcome in this population.

INTRODUCTION

Diaphragm dysfunction has become a leading concern in mechanically ventilated patients because of its high prevalence[1–4] and its association with negative clinical outcomes. In particular, its presence in this population has been associated with the increased duration of mechanical ventilation (MV),[5 6] weaning failure[3 7 8] and death.[1 9] Accordingly, a reliable and simple diagnostic method to quantify diaphragm function in the intensive care unit (ICU) setting would be a desirable tool for clinicians in order to guide the management of MV, evaluate prognosis and possibly improve the outcome of patients with diaphragm dysfunction.[10–12]

The reference method to evaluate diaphragm function remains the measurement of the negative intrathoracic pressure generated by bilateral stimulation of the phrenic nerves.[13] However, this technique requires specialised expertise and is time-consuming, and is therefore impractical for routine use in the clinical setting. Recently, ultrasound has emerged as a promising technique allowing easy and rapid estimation of diaphragm function, especially in the weaning period.[14–18] Diaphragm thickness has been shown to decline in response to prolonged MV, a finding that presumably reflects diaphragmatic fibre atrophy.[19] The inspiratory thickening of the diaphragm has been more extensively correlated with relevant outcomes such as weaning failure and has been proposed as a dynamic marker of diaphragm function.[20]

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However, these indices have not been directly compared with an established marker of diaphragm function.

In light of these findings, our objectives were to (1) study the relationship between ultrasound-derived markers of diaphragm function and negative intrathoracic pressure generated by stimulation of the phrenic nerves (diaphragm twitch) in critically ill patients receiving MV, (2) establish which ultrasound-derived marker is more reliable at quantifying diaphragm function and (3) evaluate whether ultrasound-derived markers of diaphragm function are associated with clinical prognosis.

Some of the data from this study have already been published as an abstract.[21]

PATIENTS AND METHODS

The study was conducted from November 2014 to June 2015 in a 10-bed ICU within an 1800-bed university hospital. The protocol was approved by the Comité de Protection des Personnes Ile de France VI. Informed consent was obtained from patients or their relatives. Thirty-five patients from this study were also enrolled in a previous study by our group.[22]

Patients

Patients were eligible for inclusion as soon as intubation was completed and if they had an expected duration of MV of >24 hours. Exclusion criteria were: contraindications to magnetic stimulation of the phrenic nerves (cardiac pacemaker/defibrillator, cervical implants), suspicion of underlying hemidiaphragm paresis (defined as an elevation of >2.5 cm of one hemidiaphragm compared with the other on chest radiograph), pre-existing neuromuscular disorders, cervical spine injury, pregnancy, age <18 years and decision to withhold life-sustaining treatment.

Protocol

Diaphragm function was assessed with two techniques: (1) measurement of pressure generating capacity in response to bilateral magnetic stimulation of the phrenic nerves and (2) ultrasound measurement of diaphragm thickness, excursion (EXdi) and thickening fraction (TFdi). Whenever possible, diaphragm assessment was performed for each patient at two time points: (1) within 24 hours of intubation, while patients were receiving assist-control ventilation (ACV) ('initiation of mechanical ventilation') and (2) as soon as patients could sustain pressure support ventilation (PSV, termed 'switch to PSV') for at least 1 hour (see online supplemental material, for description of the criteria used to assess tolerance to PSV). When initiated, pressure support was titrated to target a tidal volume of 6–8 mL/kg ideal body weight.

Diaphragm assessment

Diaphragm assessment was performed at the aforementioned time points unless a transient condition compromising the reliability of the measurements was present. These conditions were (1) the use of neuromuscular blocking agents within the preceding 24 hours (except for succinylcholine used during rapid-sequence intubation) and (2) factors interfering with phrenic nerve stimulation (multiple functioning chest drains, high intrinsic positive end-expiratory pressure (PEEP), see below).

Phrenic nerves stimulation

The pressure generating capacity of the diaphragm was assessed in terms of the change in endotracheal tube pressure induced by bilateral anterior magnetic phrenic nerve stimulation (Ptr,stim), as already described[4 23 24] (see online supplemental material). Stimulations were delivered at the maximum intensity allowed by the stimulator, which has been showed to result in supramaximal stimulation in the majority of cases.[1 4 9 24 25]

Ultrasound assessment of diaphragmatic thickness, EXdi and thickening

Ultrasound measurements were performed by one of the two first authors. Measurements were initially attempted on both hemidiaphragms, but evaluation of the left side was abandoned after the first 25 patients because of lower interobserver agreement (see online supplemental material, e-table 1). The measurement of EXdi was added to the protocol 3 months after the beginning of the study, by which time 51 patients had already been recruited. The interobserver reliability of the ultrasound measurements of the right hemidiaphragm between the two authors has already been reported, with intraclass correlation coefficients for the measurement of end-expiratory and end-inspiratory diaphragm thickness and diaphragm TFdi all >0.87.[22]

Assessment of diaphragm thickness, EXdi and thickening was performed using a 4–12 MHz linear array transducer (Sparq ultrasound system, Phillips, Philips Healthcare, Andover, Massachusetts, USA) while patients remained connected to the ventilator. As previously reported,[26] the probe was placed perpendicular to the right chest wall, at the midaxillary line between the 9th and 10th right intercostal spaces (at the level of the zone of apposition) and the diaphragm was identified as a three-layered structure comprising two hyperechoic lines representing the pleural and peritoneal membranes and a middle hypoechoic layer representing the diaphragmatic muscle. Using M-mode at a sweep speed of 10 mm/s, at least three breathing cycles were recorded. Diaphragm thickness was measured at end-expiration and end-inspiration using electronic callipers. TFdi was calculated as ((end-inspiratory thickness – end-expiratory thickness)/end-expiratory thickness). Three uninterrupted and undisturbed breathing cycles were evaluated, and the average of the individual values was reported. Diaphragm EXdi was measured using M-mode, by placing the probe in the right subcostal region and targeting the beam at the highest point of the diaphragmatic dome.[26]

Clinical data collection

Demographic and physiological variables and medication were recovered from the medical charts of the patients. Sepsis was identified according to current guidelines.[27] The duration of MV, time to successful extubation, ICU and hospital stay, and ICU and hospital mortality were recorded. We defined successful extubation as extubation not followed by re-intubation within 48 hours.

Outcomes

Total duration of MV and ICU stay, remaining duration of MV after measurement at switch to PSV and ICU and hospital death were used as clinical outcomes. Predictor variables are listed in the Statistical analysis section.

Statistical analysis

Normality of the data was evaluated with the Kolmogorov-Smirnov test. Continuous variables are presented as median and IQR and categorical variables are expressed as absolute and relative frequencies. Mixed linear regression analyses were used to compare variables measured at initiation of MV to those measured at switch to PSV. t-tests, Mann-Whitney U tests or χ^2 tests, where appropriate, were used to compare

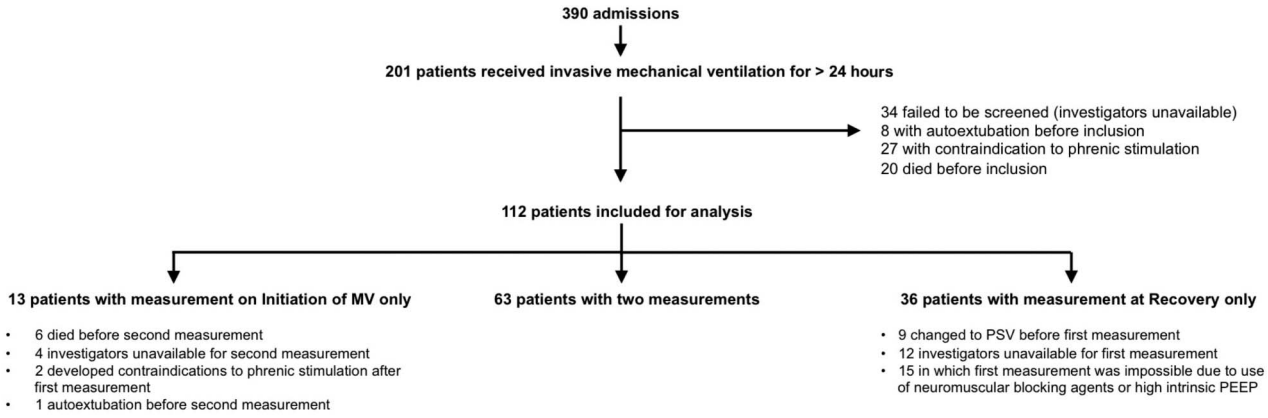

Figure 1 Study flow chart. MV, mechanical ventilation; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation.

outcomes between subgroups of patients. Relationships between diaphragm thickness, EXdi, TFdi and Ptr,stim were assessed using linear regression analysis and Spearman's correlation. Receiver operating characteristic (ROC) curve analyses were performed to identify optimal cut-off values of diaphragm thickness, EXdi and TFdi in predicting diaphragm dysfunction, and these estimates were cross-validated using bootstrapping with 1000 replications. Diaphragm dysfunction was defined as Ptr, stim<11 cm H_2O.[1–4 13]

To assess the prognostic value of diaphragm measurements, univariate analyses were performed to evaluate the relationship between clinically relevant variables and selected outcomes. Predictor variables included age, gender, COPD, diabetes, cirrhosis, tobacco smoking, Sepsis-related Organ Failure Assessment Score on admission, PEEP level, tidal volume, respiratory rate, arterial pO2 (PaO_2)/fraction of inspired oxygen (FiO_2) ratio, arterial pCO2, Ptr,stim, diaphragm thickness and TFdi. Then, for each outcome, two separate multiple linear regressions or binary logistic regressions were performed. Ptr, stim and TFdi were each entered into separate multivariate analyses, along with other variables with a p value of <0.05 in univariate analysis, to identify independent predictors of clinical outcomes.

Statistical significance was defined as p≤0.05. Analyses were performed using SPSS V.21 (SPSS, Chicago, Illinois, USA).

RESULTS

Population

During the study period, 390 patients were admitted to the ICU (figure 1). Among them, 112 patients met inclusion criteria and were included in the study. Characteristics of patients on inclusion are displayed in table 1.

Seventy-six patients were studied at initiation of MV (under ACV, of which 68 did not spontaneously trigger the ventilator) and 99 at time to switch to PSV. Characteristics of the patients at these two time points are presented in table 2.

Additional description of the patients according to the number of measurements performed is displayed in the online supplemental material (e-table 2). At switch to PSV, patients were receiving a median pressure support level of 10 (8–11) cm H_2O, and TFdi was significantly correlated to tidal volume, even after controlling for the level of pressure support (partial correlation coefficient 0.54, p<0.001). The prevalence of diaphragm dysfunction was 77% at initiation of MV and 68% at switch to PSV. EXdi was measured in 22 patients at initiation of MV and 50 patients at switch to PSV.

Table 1 Characteristics of the study population

	n=112
Gender, men	76 (68)
Age, years	62 (49–71)
BMI, kg/m^2	24 (22–29)
Tobacco smoking, n (%)	48 (43)
Comorbidities	
COPD, n (%)	24 (21)
Diabetes, n (%)	24 (21)
Cirrhosis, n (%)	17 (15)
Sepsis on admission to ICU, n (%)	51 (46)
SAPS 2	55 (33–71)
Primary indication for mechanical ventilation	
Shock, n (%)	52 (46)
Coma, n (%)	25 (22)
Acute respiratory failure, n (%)	37 (32)

Continuous variables are presented as median (IQR) and categorical variables as absolute and relative frequency.
BMI, body mass index; ICU, intensive care unit; SAPS 2, Simplified Acute Physiology Score.

Relationship between Ptr,stim and ultrasound measurements

At initiation of MV, there was no relationship between Ptr,stim and diaphragm thickness (β=−0.17, p=0.16, Spearman's r=−0.13, 95% CI −0.35 to 0.10, p=0.28), or TFdi (β=−0.09, p=0.46, Spearman's r=−0.09, 95% CI −0.31 to 0.14, p=0.45) (figure 2). There was also no relationship between Ptr,stim and EXdi (β=0.05, p=0.81, Spearman's r=0.10, 95% CI −0.13 to 0.32, p=0.66) (e-figure 1).

At switch to PSV, there was no relationship between Ptr,stim and diaphragm thickness (β=−0.01, p=0.92, Spearman's r=−0.03, 95% CI −0.23 to 0.17, p=0.80) (figure 3). However, there were statistically significant associations and very strong and moderate correlations, respectively, between Ptr,sim and TFdi (β=0.89, p<0.001, Spearman's r=0.87, 95% CI 0.81 to 0.91, p<0.001) (figure 3) and EXdi (β=0.28, p=0.05, Spearman's r=0.45, 95% CI 0.20 to 0.65, p=0.001) (e-figure 1).

Diagnosis of diaphragm dysfunction using ultrasound markers

At initiation of MV, neither diaphragm thickness, EXdi nor TFdi could reliably identify the presence of diaphragm

Table 2 Characteristics of the patients according to number and time of measurements

	Initiation of MV (n=76)	Switch to PSV (n=99)	p Value
Days from intubation, days	1 (1–1)	4 (2–6)	<0.001
Ventilator mode			
Assist-control ventilation	76 (100)	0 (0)	–
Pressure support ventilation	0 (0)	99 (100)	–
Ventilatory variables			
Spontaneous triggering of the ventilator,* n (%)	8 (11)	99 (100)	<0.001
Pressure support level, cm H_2O	NA	10 (8–11)	–
PEEP level, cm H_2O	5 (5–8)	5 (5–7)	0.26
Tidal volume, mL/kg ideal body weight	6.4 (6.1–7.0)	7.1 (6.0–8.4)	<0.001
Respiratory rate, breaths/min	21 (18–23)	21 (19–23)	0.99
Arterial blood gases			
pH	7.36 (7.28–7.44)	7.44 (7.37–7.46)	<0.001
PaO_2/FiO_2 ratio, mm Hg	222 (163–280)	260 (209–333)	0.02
$PaCO_2$, mm Hg	40 (33–47)	38 (34–47)	0.91
Blood lactate, mmol/L	1.8 (1.1–2.8)	1.5 (1.1–1.9)	0.01
Bicarbonates, mmol/L	22 (18–25)	25 (22–28)	<0.001
Mean arterial pressure, mm Hg	78 (70–89)	81 (71–96)	0.25
Heart rate, bpm	87 (71–103)	90 (78–104)	0.17
Active medication			
Benzodiazepines, n (%)	33 (43)	34 (34)	0.12
Propofol, n (%)	38 (50)	47 (48)	0.58
Opiates, n (%)	53 (70)	47 (48)	0.004
Norepinephrine, n (%)	46 (61)	36 (36)	0.001
Corticosteroids, n (%)	13 (17)	13 (13)	0.20

Continuous variables are presented as median (IQR) and categorical variables are expressed as absolute and relative frequency.
*In assist-control ventilation, spontaneous triggering of the ventilator was considered present when the observed respiratory rate was higher than the respiratory rate set on the ventilator.
FiO_2, fraction of inspired oxygen; MV, mechanical ventilation; NA, not applicable; $PaCO_2$, arterial pCO2; PaO_2, arterial pO2; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation.

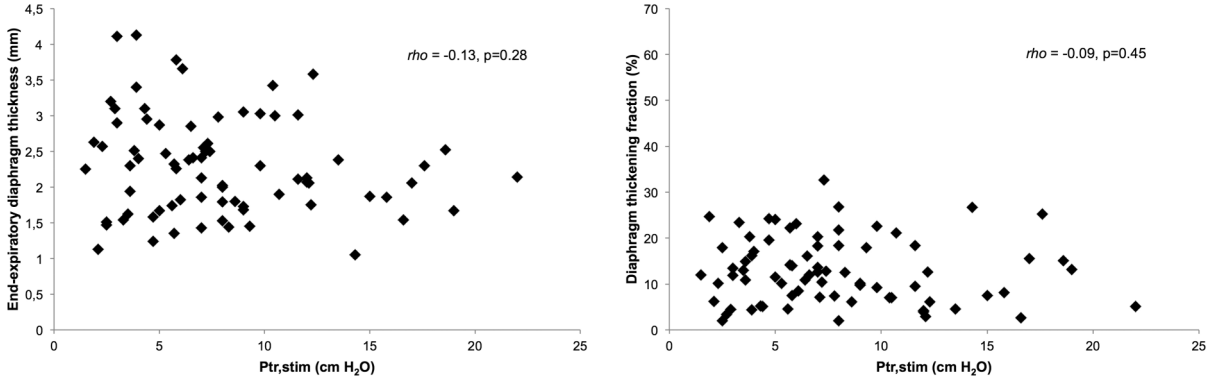

Figure 2 Correlation analysis between changes in endotracheal tube pressure induced by bilateral anterior magnetic phrenic nerve stimulation during manual airway occlusion (Ptr,stim) and end-expiratory diaphragm thickness (left panel) and thickening fraction (right panel) measured by ultrasound on initiation of mechanical ventilation.

dysfunction (area under ROC curve 0.58, 95% CI 0.44 to 0.72, p=0.33, 0.60, 95% CI 0.35 to 0.86, p=0.43 and 0.63, 95% CI 0.46 to 0.79, p=0.12, respectively) (figure 4 and e–figure 2). At switch to PSV, TFdi could reliably identify diaphragm dysfunction (area under ROC curve 0.91, 95% CI 0.85 to 0.97, p<0.001), whereas diaphragm thickness and EXdi could not (area under ROC curve 0.55, 95% CI 0.43 to 0.67, p=0.44 and 0.63, 95% CI 0.48 to 0.78, p=0.12, respectively) (figure 4 and e–figure 2). At switch to PSV, a TFdi <29% (bootstrapped 95% CI 25% to 30%) could detect diaphragm dysfunction with a sensitivity of 85% and specificity of 88%, with positive and negative values of 93% and 74%, respectively.

Comparison of the prognostic values of Ptr,stim and TFdi

The prognostic values of Ptr,stim and TFdi were measured and compared at switch to PSV since it was the only time point at which an ultrasound measurement could reliably predict diaphragm dysfunction. The threshold value of 29% for the identification of diaphragm dysfunction had a similar prognostic value as Ptr,stim <11 cm H_2O, with both being associated with worse outcome regarding length of MV and ICU stay, remaining length of MV after the measurement, and ICU and hospital mortality (table 3).

e-table 3 shows the factors associated with remaining duration of MV identified by univariate analysis. By multiple linear regression model analysis, two of these factors independently

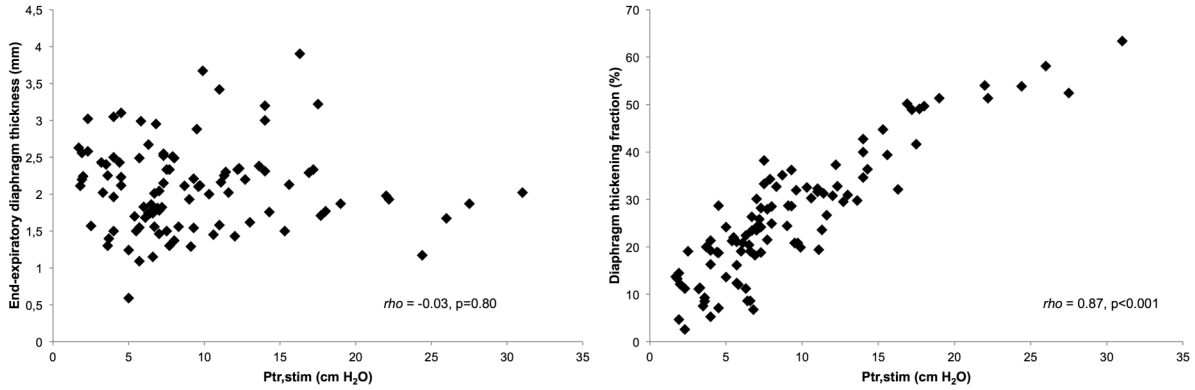

Figure 3 Correlation analysis between changes in endotracheal tube pressure induced by bilateral anterior magnetic phrenic nerve stimulation during manual airway occlusion (Ptr,stim) and end-expiratory diaphragm thickness (left panel) and diaphragm thickening fraction (right panel) measured by ultrasound at the moment of switch to pressure-support ventilation.

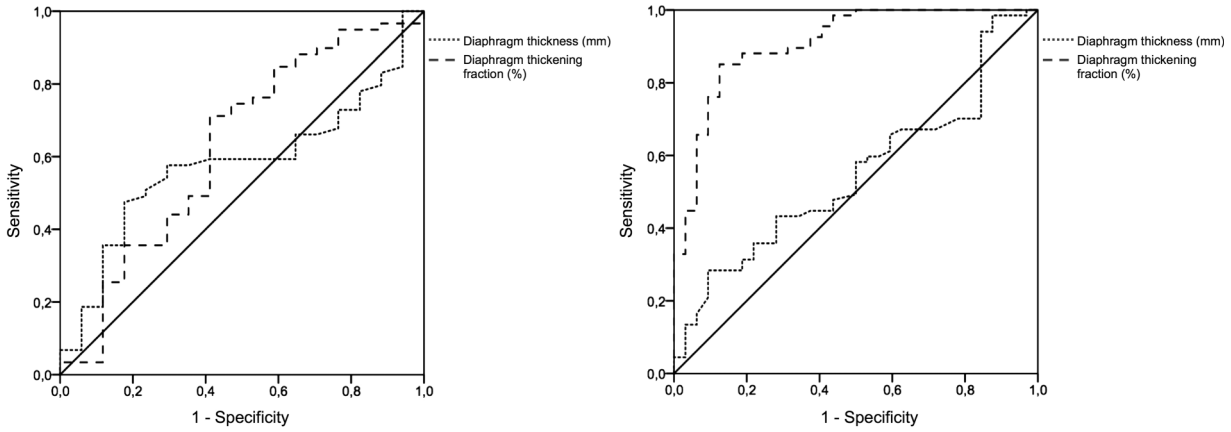

Figure 4 Receiver operating characteristic (ROC) curve for the diagnosis of diaphragm dysfunction (defined as a change in endotracheal tube pressure induced by bilateral anterior magnetic phrenic nerve stimulation <11 cm H_2O) for end-expiratory diaphragm thickness (dotted line) and diaphragm thickening fraction (dashed line), on initiation of mechanical ventilation (left panel) and switch to pressure support ventilation (right panel).

Table 3 Clinical outcomes according to the presence of diaphragm dysfunction at switch to pressure support ventilation

	Diaphragm dysfunction defined as Ptr,stim <11 cm H_2O			Diaphragm dysfunction defined as TFdi <29%		
	Yes (n=67)	No (n=32)	p Value	Yes (n=61)	No (n=38)	p Value
Length of ICU stay, days	10 (6–16)	6 (3–12)	0.05	10 (6–17)	6 (4–11)	0.02
Length of MV, days	7 (5–11)	4 (1–7)	0.04	7 (5–12)	5 (2–8)	0.02
ICU deaths, n (%)	15 (22)	2 (6)	0.05	16 (26)	1 (3)	0.002
Hospital deaths, n (%)	18 (27)	3 (9)	0.05	19 (31)	2 (5)	0.002
Remaining days of MV after measurement, days	3 (1–5)	0 (0–1)	0.04	2 (1–5)	0 (0–3)	0.04

Analyses were performed on the subset of patients with a measurement performed at the time of switch to PSV (n=99).
Continuous variables are presented as median (IQR) and categorical variables are expressed as absolute (relative) frequency.
ICU, intensive care unit; MV, mechanical ventilation; PSV, pressure support ventilation; Ptr,stim, twitch pressure in response to bilateral phrenic nerve stimulation; TFdi, thickening fraction of the diaphragm.

predicted remaining duration of MV: Ptr,stim and TFdi. e-table 4 shows the factors associated with ICU mortality identified by univariate analysis. By multiple linear regression model analysis, three of these factors independently predicted ICU mortality: Ptr,stim, TFdi and PaO_2/FiO_2 ratio. e-table 5 shows the factors associated with hospital mortality identified by univariate analysis. By multiple linear regression model analysis, three of these factors independently predicted remaining duration of MV: Ptr, stim, TFdi and PaO_2/FiO_2 ratio.

DISCUSSION

Our main findings are as follows: in a cohort of mechanically ventilated patients (1) right diaphragm thickness was unrelated to diaphragm pressure generation capacity, (2) at the moment of switch to PSV, the thickening ratio of the right diaphragm was a reliable marker of diaphragm function and (3) diaphragm dysfunction at switch to PSV was associated with adverse clinical outcomes. This is the first study to systematically investigate the relationship between ultrasound-derived

markers of diaphragm function and an established method of diaphragm contractility evaluation.

These results help to clarify the validity of ultrasound-derived measurements of diaphragm function in the ICU population, delineate the circumstances under which these measurements should be performed in order to truly represent diaphragm function and suggest that the prognostic value of diaphragm function in this population is possible to assess using ultrasound.

Relationship between diaphragm thickness and Ptr,stim

Our finding that diaphragm thickness was unrelated to its pressure generation ability can seem surprising, since a decrease in muscle thickness could intuitively be expected to translate into muscle weakness. When measured serially, diaphragm thickness has been shown to decrease with ongoing MV,[18 28] presumably reflecting muscle atrophy and weakness. However, several findings cast doubt on the putative relationship between diaphragm thickness and its strength. In a study investigating the evolution of diaphragm thickness of critically ill patients during their first week of MV,[18] low diaphragm contractile activity (estimated using TFdi) was associated with both a decline and an increase in diaphragm thickness. It is possible that an increase in diaphragm thickness may therefore represent a pathological process such as tissue oedema, rather than an increase in functional muscle mass. A report on the distribution of diaphragm thickness in a large cohort of healthy subjects showed that a value of 0.17 cm represented the lower limit of normal of the distribution for the right hemidiaphragm.[29] However, among patients with long-standing phrenic paresis or diaphragmatic myositis, a proportion of patients present with diaphragm thickness values above this threshold.[30–33] In light of this, we believe that these findings, coupled with our own, cast serious doubt on the validity and usefulness of diaphragm thickness as a relevant marker of diaphragm function, at least in the ICU setting.

Relationship between diaphragm TFdi and Ptr,stim

In contrast, we found a strong relationship between diaphragm twitch pressure and TFdi, but only when measured at switch to PSV. We hypothesise that the reason we observed such a strong correlation at that moment but not at the initiation of MV was the presence of a much higher prevalence of spontaneous breathing effort in the former, but not in the latter. Indeed, it seems intuitive to suppose that without active breathing efforts, TFdi cannot be expected to act as a dynamic physiological estimator of diaphragm function. Interestingly, some degree of diaphragm thickening could still be observed in the majority of patients under ACV, although the mean value was much lower than in patients under PSV. This finding should alert clinicians to the fact that the observation of a non-zero diaphragm thickening in patients under MV should not systematically be considered a reliable estimator of the underlying Ptr,stim. In this regard, our findings echo those of others, in which even patients under neuromuscular blockade showed a small but measurable degree of diaphragm thickening.[20] In these patients, and in patients under ACV, it is possible that the passive inflation of the lung and mechanical displacement of the diaphragm, as well as weak or partial respiratory efforts may be partly responsible for the observed thickening of the diaphragm, especially at higher lung volumes. In addition, it should be kept in mind that significant alterations in end-expiratory diaphragm thickness caused by atrophy or oedema may alter the value of TFdi, which could impair its relationship with Ptr,sim, although this phenomenon may be mitigated if end-expiratory and end-inspiratory thicknesses are similarly affected. Further studies on this issue are required.

A recent study which compared various markers of diaphragm activity in the prediction of weaning outcome also found a significant relationship between TFdi and diaphragm function measured using magnetic stimulation of the phrenic nerves, although it was lower than in our study.[34]

Relationship between EXdi and Ptr,stim

EXdi was not correlated to Ptr,stim at the initiation of MV, but only moderately correlated to Ptr,stim at switch to PSV. This finding may be related to the fact that EXdi is dependent on the degree of active diaphragm contraction, and on the passive displacement of the diaphragm induced by the ventilator.

Relationship between diaphragm function and outcome

The finding that diaphragm function is related to length of MV, duration of stay and mortality of critically ill patients is not new, but had until now mainly been evaluated using phrenic nerve stimulation techniques,[1 5 6] which cannot be routinely used in clinical practice. Our study is the first to report the significant relationship between TFdi and clinically relevant outcomes such as length of MV and ICU and hospital stay and mortality. Of note, our finding that a higher TFdi value is associated with a decreased remaining duration of MV echoes the findings of others, who showed that TFdi could act as an important predictor of weaning outcome.[14 15 17 22] Our results add the important finding that these clinically important outcomes can be accurately assessed using ultrasound, a simple, non-invasive and rapid technique that is widely available. It remains unclear whether diaphragm dysfunction itself has a causative effect on the prognosis of ICU patients, or if its presence should be seen as an organ dysfunction, implying a more severe underlying disease. Our results do not allow that question to be answered, but fuel the need for additional studies evaluating the putative role of diaphragmatic function in the evolution of ICU patients.

Strength and limitations

The strengths of our study include the inclusion of a large number of patients, allowing for a meaningful comparison of ultrasound variables with the reference method. In addition, the systematic use of bilateral magnetic stimulation of the phrenic nerves as a reference method lends strength to our results, as this technique allows an objective and non-volitional evaluation of diaphragm function that is more reliable than other methods such as the measurement of maximal inspiratory pressures, especially in the ICU setting.[35] We measured TFdi during tidal breathing, which has the advantage of being non-volitional and possible to use even in sedated or non-cooperative patients. Our choice of performing measurements at the moment of switching to PSV was based our belief that this moment had clinical relevance, as it likely represents an individualised moment where patients begin to recover from their underlying illness. Our findings that diaphragm function measured at this time point had prognostic implications support the clinical usefulness of the evaluation of diaphragm function even after several days of MV.

We acknowledge several limitations to our study. First, the conditions in which we performed our measurements must be taken into account when generalising our results. When measured under MV, TFdi is related to neural respiratory drive, and can be influenced by the level of diaphragm unloading and therefore by the level of assistance provided by the ventilator.[36 37] We did not formally measure neural respiratory drive to the diaphragm or work of breathing in our study, and

although it is possible that these variables may have influenced our measurement of TFdi, we believe this must not have been a significant confounding factor because of (1) the fact that most patients under ACV had no spontaneous breathing efforts and (2) the fact that patients under PSV received individualised pressure support levels targeted at a tidal volume that minimised situations of increased or decreased respiratory drive such as overassistance or underassistance. These subjects therefore probably displayed a relatively homogeneous degree of respiratory drive. We need to emphasise, however, that our results may not be generalisable to a population in which the prevailing ventilator settings or respiratory state result in abnormally increased or decreased work of breathing such as respiratory distress, weaning trials or in situations of overassistance and underassistance. Second, the use of a Ptr,stim cut-off value of 11 cm H_2O to define the presence of diaphragmatic dysfunction can be questioned, but this value has been reported as indicative of diaphragm weakness.[1 38] Third, our study was performed in a medical ICU. As such, it is possible that our results would not be directly applicable to patients recovering from surgery, especially major thoracic or abdominal surgeries, which could alter the measurement of Ptr,stim and TFdi. Fourth, as we did not formally confirm the supramaximal nature of phrenic stimulation in our patients, we cannot rule out that Ptr,stim was underestimated in some of them, which could have influenced our results. In the present study, we deliberately opted to omit supramaximality testing to avoid inducing excessive discomfort. Although we acknowledge this issue as requiring caution, we note that the stimulation protocol that we used has been reported to produce supramaximal stimulations in many cases, including in ICU patients.[4 9 24 25] We also wish to point out that independently of whether the stimulations delivered were supramaximal or not, the Ptr,stim threshold that we used was significantly and independently associated with adverse clinical outcomes. From a pragmatic point of view and with regards to the transposability of our results, this means that performing phrenic stimulation at the maximal output of the device we used can provide clinically useful data. Fifth, from a statistical viewpoint, the comparison of two ROC curves should be made with caution when they are crossing. However, this is unlikely to be significant in our results as (1) both diaphragm thickness and TFdi had non-significant AUROC curves for the prediction of diaphragm dysfunction under ACV and (2) under PSV, where the comparison is most relevant, the curves do not cross. Finally, we limited our ultrasound evaluation to the right hemidiaphragm because of the higher interobserver reliability of observations on this side, which is probably related to the better acoustic window provided by the underlying liver tissue.

CONCLUSION

In a cohort of critically ill, mechanically ventilated patients, we found no significant relationship between diaphragm thickness and its contractile capacity, suggesting that diaphragm thickness should not be used as an estimator of diaphragm contractility in the ICU setting. In contrast, we found a strong relationship between TFdi and Ptr,stim, when measured in patients receiving a partial mode of ventilator assistance, suggesting that TFdi can be used to diagnose diaphragm dysfunction in this setting. This is all the more relevant since the presence of such a dysfunction at this stage of ICU stay was associated with a poorer prognosis. Taken together, these results provide evidence that TFdi can be used as a reliable estimator of diaphragm function in this setting. Beyond prognostic purposes, this could prove useful for the management of indications and the follow-up of putative therapeutic approaches such as inspiratory muscle training[39] or diaphragm pacing.[11 40]

Contributors B-PD, MD and AD designed the study. MD coordinated the study. MD, B-PD, SD and JM were responsible for patient screening, enrolment and follow-up. MD, B-PD, TS and AD analysed the data. B-PD, MD, TS and AD wrote the manuscript. All authors had full access to all of the study data, contributed to draft the manuscript or revised it critically for important intellectual content, approved the final version of the manuscript, and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests B-PD has received honoraria from GlaxoSmithKline, Boehringer Ingelheim, Astra Zeneca and Roche. AD has signed research contracts with Covidien, Maquet and Philips; he has also received personal fees from Covidien and MSD. MD received personal fees from Pulsion Medical System and Astra Zeneca. Relevant to the present study, TS has received personal fees from Lungpacer and is a member of the board of a research association that has received, over the past 10 years, unrestricted research grants from Maquet, Hamilton, Covidien and Philips; he is the head of a research unit (UMRS 1158) that has signed research contracts with Air Liquide Medical Systems, France; he is listed as inventor or co-inventor on several patents, granted or pending, describing a brain-ventilator interface.

Ethics approval Comité de Protection des Personnes Ile de France VI.

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Ultrasound evaluation of diaphragm function in mechanically-ventilated patients: comparison to phrenic stimulation and prognostic implications

Bruno-Pierre Dubé[1,2], MD, Martin Dres[1,3], MD, Julien Mayaux[3], MD, Suela Demiri[3], MD, Thomas Similowski[1,3], MD, PhD and Alexandre Demoule[1,3], MD, PhD

[1]Sorbonne Universités, UPMC Univ Paris 06, INSERM, UMRS1158 Neurophysiologie respiratoire expérimentale et clinique, Paris, France

[2]Département de médecine, service de pneumologie, hôpital Hôtel-Dieu du Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, Québec, Canada

[3]AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie et Réanimation Médicale (*Département "R3S"*), F-75013, Paris, France

Online supplement

Patients and methods

The study was conducted from November 2014 to June 2015 in a 10-bed ICU within an 1800-bed university hospital. The protocol was approved by the Comité de Protection des Personnes Ile de France VI. Informed consent was obtained from the patients or their relatives. Thirty-five patients from the present study were also enrolled in a previously published study by our group.[1]

Patients

Patients were eligible for inclusion as soon as intubation was completed and if they had an expected duration of MV of >24h. Exclusion criteria were: contraindications to magnetic stimulation of the phrenic nerves (cardiac pacemaker or defibrillator, cervical implants), suspicion of underlying hemidiaphragm paralysis (defined as an elevation of >2·5 cm of one hemidiaphragm compared to the other on chest radiograph), pre-existing neuromuscular disorders, cervical spine injury, pregnancy, age <18 years and a decision to withhold life-sustaining treatment.

Protocol

Diaphragm function was assessed with two techniques: 1) measurement of pressure generating capacity in response to bilateral magnetic stimulation of the phrenic nerves and 2) ultrasound measurement of diaphragm thickness, excursion and thickening fraction. Whenever possible, diaphragm assessment was performed for each patient at two time points: 1) within 24 hours of intubation, while patients were receiving assist-control ventilation ("initiation of MV") and 2) as soon as patients could sustain pressure support ventilation (PSV, termed "switch to PSV") for least 1 hour with a PS ≤24 cmH_2O, a positive end-expiratory pressure (PEEP) ≤12 cmH_2O, a total level of inspiratory pressure <30 cmH_2O, a respiratory rate ≤24/min, and tidal volume ≥5 ml/kg ideal body weight, without signs of labored breathing, as defined by retractions or recessions - sucking in of the skin around the ribs and the top of the sternum, or prominent use of accessory respiratory muscles. These criteria are those that are routinely used by attending physicians in our ICU to evaluate, on a daily basis, the possibility of

switching patients to PSV. When initiated, pressure support is titrated to target a tidal volume of 6–8 ml/kg ideal body weight.

Diaphragm assessment

Diaphragm assessment was performed at the aforementioned time points unless a transient condition compromising the reliability of the measurements was present. These conditions were 1) the use of neuromuscular blocking agents within the preceding 24 hours (with the exception of succinylcholine used during rapid-sequence intubation), and 2) factors interfering with phrenic nerve stimulation (multiple functioning chest drains, high intrinsic positive end expiratory pressure, *see* below).

Phrenic nerves stimulation

The pressure generating capacity of the diaphragm was assessed in terms of the change in endotracheal tube pressure induced by bilateral anterior magnetic phrenic nerve stimulation (Ptr,stim), as already described.[2-4] Two figure-of-eight coils connected to a pair of Magstim 200 stimulators (The Magstim Company, Dyfed, UK) were positioned immediately posterior to the sternomastoid muscles at the level of the cricoid cartilage. Stimulations were delivered at the maximum intensity allowed by the stimulator, which has been showed to result in supramaximal stimulation in the majority of cases.[2 4-7] Patients were studied in a standardized semi-recumbent position, as follows: end-expiratory pressure was set to zero and the patient was allowed to exhale during an end-expiratory pause until expiratory airflow reached zero (relaxed equilibrium volume of the respiratory system). The absence of active respiratory efforts in response to stimulation

was determined by checking the stability of the airway pressure signal. The endotracheal tube was then briefly disconnected and manually occluded. When the absence of intrinsic PEEP was confirmed by ensuring that endotracheal pressure tracing at that moment was zero, bilateral anterolateral magnetic stimulation was delivered. Measurements were repeated at least three times and the mean of all valid measurements was reported. Ptr,stim was defined as the amplitude of the negative pressure wave following stimulation, taken from baseline to peak. It was measured at the proximal tip of the endotracheal tube, using a linear differential pressure transducer (MP45 ±100 cmH2O, Validyne, Northridge, Calif., USA). The pressure signal was sampled and digitized (MP30, Biopac Systems, Santa Barbara, Calif., USA or Powerlab, AD Instruments, Bella Vista, Australia) for subsequent data analysis.

Ultrasound assessment of diaphragmatic thickness, excursion and thickening

Ultrasound measurements were performed by one of the two first authors. Measurements were initially attempted on both hemidiaphragms, but evaluation of the left side was abandoned after the first 25 patients because of lower inter-observer agreement (*see* online supplemental material, e-table 1). The measurement of diaphragmatic excursion was added to the protocol three months after the beginning of the study, by which time 51 patients had already been recruited. The inter-observer reliability of the ultrasound measurements of the right hemidiaphragm between the two authors has already been reported, with intra-class correlation coefficients for the measurement of end-expiratory and end-inspiratory diaphragm thickness and diaphragm thickening fraction all >0.87.[1]

Ultrasound assessment of diaphragm thickness, excursion and thickening was performed using a 4-12 MHz linear array transducer (Sparq ultrasound system, Phillips, Philips Healthcare, Andover, MA, USA) while patients remained connected to the ventilator. As previously reported,[8] the probe was placed perpendicular to the right chest wall, at the midaxillary line between the 9th and 10th right intercostal spaces (at the level of the zone of apposition) and the diaphragm was identified as a three-layered structure comprising two hyperechoic lines representing the pleural and peritoneal membranes and a middle hypoechoic layer representing the diaphragmatic muscle. Using M-mode at a sweep speed of 10 mm/s, at least three breathing cycles were recorded. Diaphragm thickness was measured at end-expiration and end-inspiration using electronic calipers. The thickening fraction of the diaphragm (TFdi) was calculated as [(end-inspiratory thickness – end-expiratory thickness)/end-expiratory thickness]. Three valid breathing cycles were recorded, and the average of the individual values was reported. Diaphragm excursion (EXdi) was measured using M-mode, by placing the probe in the right sub-costal region and targeting the beam at the highest point of the diaphragmatic dome.[8]

Clinical data collection

Demographic and physiological variables and medication were recovered from the medical charts of patients. Sepsis was identified according to current guidelines.[9] The duration of mechanical ventilation, time to successful extubation, ICU and hospital stay and ICU and hospital mortality were recorded. We defined successful extubation as extubation not followed by reintubation within 48 hours.

Outcomes

Total duration of mechanical ventilation and ICU stay, remaining duration of mechanical ventilation after measurement at switch to PSV and ICU and hospital death were used as clinical outcomes. Predictor variables are listed in the Statistical Analysis section.

Statistical Analysis

Normality of the data was evaluated with the Kolmogorov-Smirnov test. Continuous variables are presented as median and interquartile range and categorical variables are expressed as absolute and relative frequency. Mixed linear regression analyses were used to compare variables measured at initiation of mechanical ventilation to those measured at switch to PSV. T-tests, Mann-Whitney U-tests or Chi-square tests, where appropriate, were used to compare outcomes between subgroups of patients. Relationships between diaphragm thickness, EXdi, TFdi and Ptr,stim were assessed using linear regression analysis and Spearman correlation. Receiver operating characteristic (ROC) curves were performed to identify optimal cut-off values of diaphragm thickness, EXdi and TFdi in predicting diaphragm dysfunction, and these estimates were cross-validated using bootstrapping with 1000 replications. Diaphragm dysfunction was defined as Ptr,stim<11 cmH_2O.[2 5 10-12]

To assess the prognostic value of diaphragm measurements, univariate analyses were performed to evaluate the relationship between clinically relevant variables and selected outcomes. Predictor variables included age, gender, chronic obstructive pulmonary disease (COPD), diabetes, cirrhosis, tobacco smoking, Sequential Organ Failure assessment (SOFA) score on admission, positive end-expiratory pressure (PEEP) level, tidal volume, respiratory rate, mean arterial pressure, heart rate, PaO_2/FiO_2 ratio, $PaCO_2$,

Ptr,stim, diaphragm thickness and TFdi. Then, for each outcome, two separated multiple linear regression or binary logistic regression models were performed. Ptr,stim and TFdi were each entered into separate multivariate analyses, along with other variables with a *p* value of <0.05 in univariate analysis, to identify independent predictors of clinical outcomes.

Statistical significance was defined as $p \leq 0.05$. Analyses were performed using SPSS v21 (SPSS Inc., Chicago, IL).

E-tables

e-table 1. Inter-observer reliability for the measurements of left diaphragm thickness and thickening fraction

Variable	Intra-class correlation coefficient	95% confidence interval	p-value
At initiation of MV			
End-expiratory diaphragm thickness	0.72	0.27 – 0.91	0.003
Inspiratory diaphragm thickness	0.68	0.18 – 0.90	0.007
Diaphragm thickening fraction	0.24	-0.37 – 0.70	0.22
At switch to PSV			
End-expiratory diaphragm thickness	0.67	0.25 – 0.89	0.003
Inspiratory diaphragm thickness	0.58	0.06 – 0.85	0.02
Diaphragm thickening fraction	0.68	0.24 – 0.89	0.004
All measurements			
End-expiratory diaphragm thickness	0.76	0.53 – 0.89	<0.001
Inspiratory diaphragm thickness	0.72	0.45 – 0.87	<0.001
Diaphragm thickening fraction	0.44	0.06 – 0.71	0.02

MV, mechanical ventilation; PSV, pressure-support ventilation

e-table 2. Characteristics of the patients according to number and time of measurements

	Patients with a single measurement			Patients with two measurements		
	Initiation of MV	Switch to PSV	p-value	Initiation of MV	Switch to PSV	p-value
n	13	36	-	63	63	-
Ventilatory mode						
Assist-control ventilation, *n (%)*	13 (100)	0 (0)	-	63 (100)	0 (0)	-
Pressure-support ventilation, *n (%)*	0 (0)	36 (100)	-	0 (0)	63 (100)	-
Time since intubation, *days*	1 (1–1)	2 (1–4)	0.02	1 (1 – 1)	4 (3 – 7)	<0.01
Active medication						
Benzodiazepines, *n (%)*	5 (39)	19 (53)	0.52	28 (44)	15 (24)	0.02
Norepinephrine, *n (%)*	7 (54)	15 (42)	0.53	39 (61)	21 (33)	<0.01
Propofol, *n (%)*	6 (46)	24 (67)	0.32	32 (51)	23 (37)	0.15
Opiates, *n (%)*	10 (77)	24 (67)	0.73	43 (68)	23 (37)	0.001
Corticosteroids, *n (%)*	2 (15)	7 (19)	0.99	11 (18)	6 (10)	0.30
Mean arterial pressure, *mmHg*	80 (71 – 94)	83 (70 – 99)	0.34	78 (70 – 89)	80 (71 – 91)	0.67
Heart rate, *bpm*	79 (66 – 110)	85 (75 – 101)	0.98	89 (72 – 102)	91 (80 – 105)	0.08
Ventilatory variables						
Spontaneous triggering of ventilator, *yes*	1 (7)	36 (100)	<0.01	10 (16)	63 (100)	<0.01
Pressure support level, *cm H_2O*	-	8 (7 – 10)	-	-	10 (8 – 12)	-
PEEP level, *cmH_2O*	6 (5 – 8)	5 (5 – 6)	0.21	5 (5 – 8)	5 (5 – 8)	0.59
Tidal volume, *ml/kg ideal body weight*	6.6 (6.2 – 7.4)	7.0 (6.0 – 8.4)	0.30	6.3 (6.1 – 6.8)	7.3 (5.9 – 8.7)	<0.01
Respiratory rate, *br/min*	20 (18 – 23)	20 (19 – 22)	0.67	21 (19 – 22)	21 (18 – 24)	0.80
Arterial blood gases						
pH	7·32 (7.27 – 7.43)	7·44 (7·40 – 7.47)	<0.001	7.37 (7.29 – 7.44)	7.43 (7.36 – 7.45)	0.001
PaO_2/FiO_2 ratio	205 (136 – 229)	300 (215 – 407)	0.02	238 (164 – 294)	247 (202 – 309)	0.21
$PaCO_2$, *mmHg*	43 (36 – 51)	37 (34 – 41)	0.22	39 (33 – 46)	38 (34 – 49)	0.65
Blood lactates, *mmol/L*	1.9 (1.2 – 4.7)	1.4 (1.2 – 2.1)	0.003	1.7 (1.1 – 2.5)	1.5 (1.1 – 1.9)	0.05
Bicarbonates, *mmol/L*	23 (18 – 26)	25 (23 – 27)	0.06	22 (19 – 26)	24 (21 – 29)	<0.01

Continuous variables are presented as median (interquartile range) and categorical variables are expressed as absolute and relative frequency. PEEP, positive end-expiratory pressure; PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; NA, not applicable.

[a] In assist-control ventilation, spontaneous triggering of the ventilator was considered present when the observed respiratory rate was higher than the respiratory rate set on the ventilator

e-table 3. Univariate and multiple linear regression analyses for the prediction of remaining time of mechanical ventilation after switch to PSV.

Univariate regression analysis

	B	95% CI	p-value
Age	0.05	-0.03 – 0.12	0.22
Gender	0.31	-2.19 – 2.79	0.81
COPD	0.67	-2.13 – 3.47	0.64
Diabetes	1.89	-0.88 – 4.67	0.18
Tobacco smoking	1.51	-0.81 – 3.83	0.20
Cirrhosis	-1.14	-4.29 – 2.01	0.47
SOFA on admission	-0.04	-0.37 – 0.28	0.78
Variables measured at time of switch to PSV:			
PEEP	0.36	-0.38 – 1.11	0.34
Tidal volume	-0.48	-1.10 – 0.15	0.13
Respiratory rate	0.02	-0.34 – 0.37	0.93
PaO_2/FiO_2 ratio	-0.01	-0.02 - -0.01	**0.05**
$PaCO_2$	0.001	-0.13 – 0.13	0.99
Ptr,stim	-0.28	-0.46 - -0.09	**0.005**
Diaphragm thickness	-0.003	-0.02 – 0.02	0.77
TFdi	-0.11	-0.19 - -0.02	**0.02**
EXdi	0.12	-2.09 – 2.32	0.92

Multiple linear regression model (model with Ptr,stim)

	B	95% CI	p-value
PaO_2/FiO_2 ratio	-0.01	-0.02 – 0.004	0.20
Ptr,stim	-0.20	-0.40 - -0.01	**0.04**

Multiple linear regression model (model with TFdi)

	B	95% CI	p-value
PaO_2/FiO_2 ratio	-0.01	-0.02 – 0.003	0.14
TFdi	-0.10	**-0.18 - -0.01**	**0.03**

B, unstandardized regression coefficient; COPD, chronic pulmonary obstructive disease; SOFA, sequential organ failure assessment score measured on admission; PEEP, positive end-expiratory pressure; PaO_2, arterial partial pressure of oxygen; FiO2, fraction of inspired oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; Ptr,stim; twitch pressure in response to bilateral phrenic nerve stimulation; TFdi, thickening fraction of the diaphragm; EXdi, diaphragmatic excursion; CI, confidence interval.

e-table 4. Univariate and multiple logistic regression analyses for the prediction of intensive care unit mortality.

Univariate regression analysis

	OR	95% CI	p-value
Age	1.03	0.99 – 1.07	0.20
Gender	0.63	0.21 – 1.83	0.39
COPD	1.59	0.49 – 5.14	0.44
Diabetes	1.09	0.32 – 3.77	0.89
Tobacco smoking	1.14	0.40 – 3.24	0.81
Cirrhosis	1.14	0.29 – 4.52	0.86
SOFA on admission	1.22	1.06 – 1.41	**0.006**
Variables measured at time of switch to PSV:			
PEEP	1.27	0.93 – 1.72	0.13
Tidal volume	0.91	0.66 – 1.25	0.45
Respiratory rate	1.02	0.87 – 1.21	0.80
PaO_2/FiO_2 ratio	0.99	0.98 – 0.99	**0.001**
$PaCO_2$	1.04	0.98 – 1.10	0.19
Ptr,stim	0.79	0.66 – 0.94	**0.008**
Diaphragm thickness	0.99	0.98 – 1.00	0.26
TFdi	0.94	0.89 – 0.98	**0.01**
EXdi	1.18	0.27 – 5.08	0.82

Multiple logistic regression model (model with Ptr,stim)

	OR	95% CI	p-value
SOFA on admission	1.14	0.98 – 1.34	0.10
PaO_2/FiO_2 ratio	0.99	0.98 – 0.99	**0.007**
Ptr,stim	0.82	0.69 – 9.98	**0.03**

Multiple logistic regression model (model with TFdi)

	OR	95% CI	p-value
SOFA on admission	1.13	0.96 – 1.32	0.14
PaO_2/FiO_2 ratio	0.99	0.98 – 0.99	**0.006**
TFdi	0.95	0.90 – 0.99	**0.04**

OR, odds ratio; COPD, chronic pulmonary obstructive disease; SOFA, sequential organ failure assessment score measured on admission; PEEP, positive end-expiratory pressure; PaO_2, arterial partial pressure of oxygen; FiO2, fraction of inspired oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; Ptr,stim; twitch pressure in response to bilateral phrenic nerve stimulation; TFdi, thickening fraction of the diaphragm; EXdi, diaphragmatic excursion; CI, confidence interval.

e-table 5. Univariate and multiple logistic regression analyses for the prediction of hospital mortality.

Univariate regression analysis

	OR	95% CI	p-value
Age	1.03	0.99 – 1.01	0.10
Gender	0.56	0.21 – 1.50	0.25
COPD	1.55	0.52 – 4.63	0.43
Diabetes	1.12	0.36 – 3.50	0.84
Tobacco smoking	1.18	0.45 – 3.10	0.74
Cirrhosis	1.29	0.37 – 4.52	0.69
SOFA on admission	**1.22**	1.07 – 1.40	**0.004**
Variables measured at time of switch to PSV:			
PEEP	1.13	0.84 – 1.51	0.43
Tidal volume	0.83	0.61 – 1.13	0.25
Respiratory rate	1.06	0.90 – 1.24	0.48
PaO_2/FiO_2 ratio	0.99	0.98 – 0.99	**0.001**
$PaCO_2$	1.04	0.98 – 1.09	0.18
Ptr,stim	0.76	0.64 – 0.90	**0.002**
Diaphragm thickness	1.01	0.99 – 1.01	0.72
TFdi	0.93	0.88 – 0.97	**0.003**
EXdi	0.80	0.19 – 3.34	0.76

Multiple logistic regression model (model with Ptr,stim)

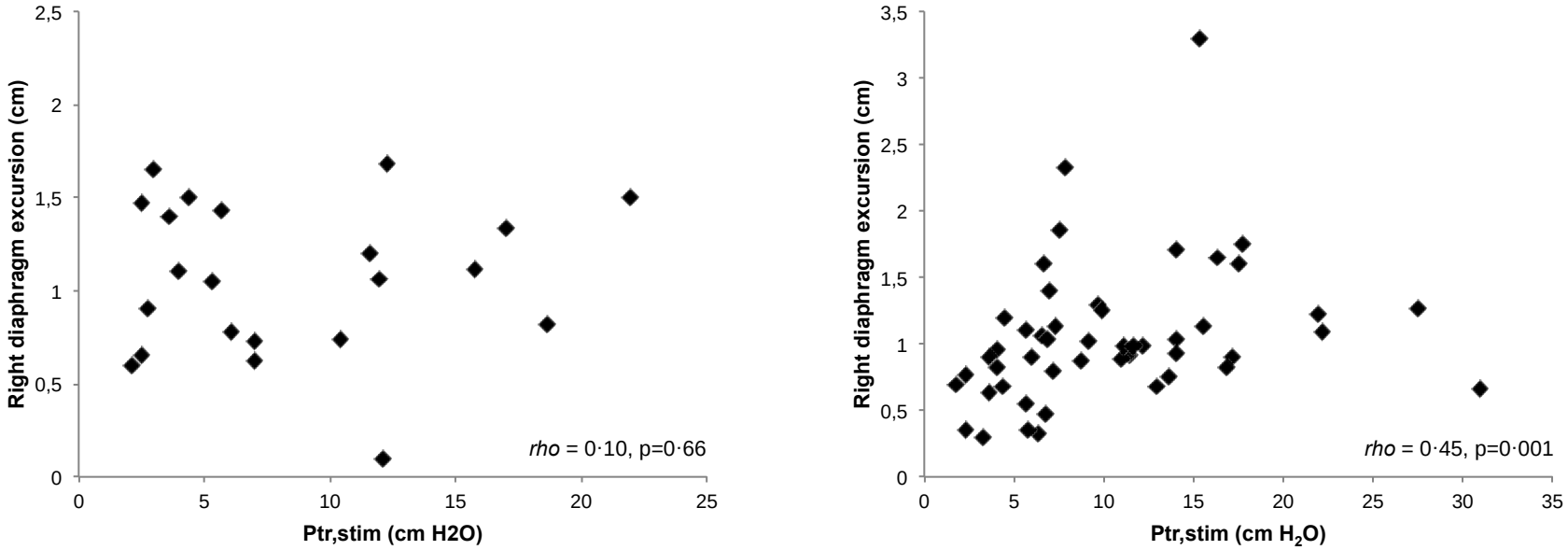
	OR	95% CI	p-value
SOFA on admission	1.15	0.99 – 1.35	0.07
PaO_2/FiO_2 ratio	0.99	0.98 – 0.99	**0.01**
Ptr,stim	0.79	0.66 – 0.94	**0.01**

Multiple logistic regression model (model with TFdi)

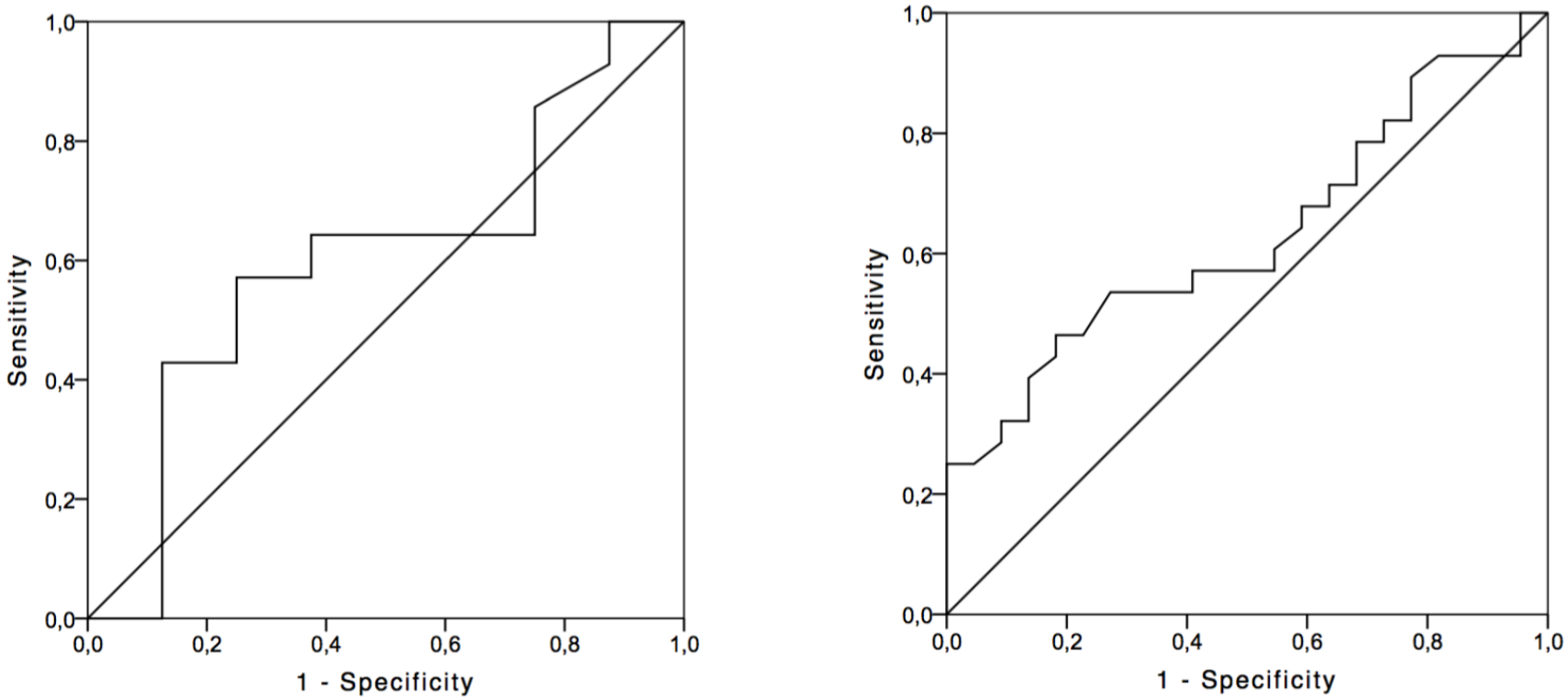
	OR	95% CI	p-value
SOFA on admission	1.14	0.97 – 1.33	0.10
PaO_2/FiO_2 ratio	0.99	0.98 – 0.99	**0.01**
TFdi	0.94	0.89 – 9.98	**0.01**

OR, odds ratio; COPD, chronic pulmonary obstructive disease; SOFA, sequential organ failure assessment score measured on admission; PEEP, positive end-expiratory pressure; PaO_2, arterial partial pressure of oxygen; FiO2, fraction of inspired oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; Ptr,stim; twitch pressure in response to bilateral phrenic nerve stimulation; TFdi, thickening fraction of the diaphragm; EXdi, diaphragmatic excursion; CI, confidence interval.

E-figures



e-figure 1. Correlation analysis between changes in endotracheal tube pressure induced by bilateral anterior magnetic phrenic nerve stimulation during manual airway occlusion (Ptr,stim) and diaphragm excursion on initiation of mechanical ventilation (right panel) and at the moment of switch to pressure-support ventilation (left panel).



e-figure 2. Receiver operating characteristic (ROC) curve for the diagnosis of diaphragm dysfunction (defined as a change in endotracheal tube pressure induced by bilateral anterior magnetic phrenic nerve stimulation < 11 cmH_2O) for diaphragm excursion on initiation of mechanical ventilation (left panel) and switch to pressure support ventilation (right panel).

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ORIGINAL

Martin Dres
Matthieu Schmidt
Alexis Ferre
Julien Mayaux
Thomas Similowski
Alexandre Demoule

Diaphragm electromyographic activity as a predictor of weaning failure

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M. Dres and M. Schmidt contributed equally to this work.

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M. Dres · M. Schmidt · A. Ferre · J. Mayaux · T. Similowski · A. Demoule (✉)
Service de Pneumologie et Réanimation médicale, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, 47-83 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France
e-mail: alexandre.demoule@psl.aphp.fr
Tel.: +33-1-42167761
Fax: +33-1-70247282

M. Schmidt · T. Similowski · A. Demoule
Université Paris 6-Pierre et Marie Curie, ER10, Paris, France

A. Demoule
UMRS 974, Institut National de la Santé et de la Recherche médicale, Paris, France

Abstract *Purpose:* To compare breathing pattern descriptors and diaphragm electromyographic activity (EAdi)-derived indices obtained from a neurally adjusted ventilatory assist catheter during a spontaneous breathing trial (SBT) in patients successfully and unsuccessfully separated from the ventilator and to assess their performance as a potential marker to discriminate these two categories of patients. *Methods:* Fifty-seven ready-to-wean patients were included in a prospective observational study. During a 30-min SBT (pressure support 7 cmH_2O, zero end expiratory pressure), tidal volume (V_T) and respiratory rate (RR) were obtained from the flow signal at baseline and at 3, 10, 20 and 30 min during the SBT. EAdi-derived indices were simultaneously computed: maximum of the EAdi ($EAdi_{max}$), area under the inspiratory curve of EAdi ($EAdi_{AUC}$), the difference between $EAdi_{max}$ and $EAdi_{min}$ ($\Delta EAdi$), $EAdi_{max}/V_T$, $EAdi_{AUC}/V_T$ and $\Delta EAdi/V_T$. Patients, successfully (success group; $n = 35$) and unsuccessfully (failure group; $n = 22$) separated from the ventilator were compared. *Results:* At baseline, the breathing pattern was similar in the two groups, whereas $EAdi_{max}$ and $EAdi_{AUC}$ were significantly lower in the success group ($p < 0.05$). In the failure group, RR and RR/V_T increased significantly during the trial, V_T decreased, whereas $EAdi_{max}$ and $EAdi_{AUC}$ did not change. At 3 min, the areas under the receiver operating characteristic-curve of RR/V_T and the EAdi-derived indices to predict weaning outcome were 0.83 for the rapid shallow breathing index (RSBI), 0.84 for $EAdi_{max}/V_T$, 0.80 for $EAdi_{AUC}/V_T$ (0.80) and 0.82 for $\Delta EAdi/V_T$. The coefficient of variation for V_T decreased in the failure group while that for $EAdi_{max}$ remained unchanged. *Conclusions:* EAdi-derived indices provide reliable and early predictors of weaning outcome. However, the performance of these indices is not better than the RR/V_T.

Keywords Mechanical ventilation · Patient–ventilator weaning · Neurally adjusted ventilator assist

Introduction

The rapid discontinuation of mechanical ventilation (MV) is a major objective of intensive care unit medicine. Current guidelines recommend that weaning from the ventilator be achieved using a two-step strategy [1]. First, there should be an assessment of the readiness of the patient for weaning; this is to be followed by the second

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step, which should be a spontaneous breathing trial (SBT) as a diagnostic test to determine the likelihood of successful extubation [2]. Various weaning predictors derived from breathing pattern analyses have been developed to enable the likelihood of a successful weaning to be assessed as early and accurately as possible [3–6]. Since the success of weaning depends on the capacity of respiratory muscle to overcome the load that impedes the respiratory system, most of these indices are surrogates of the load capacity balance. The most commonly studied of these indices is the ratio of respiratory frequency (respiratory rate) to tidal volume (RR/V_T), otherwise known as the rapid shallow breathing index (RSBI) [3], and one of the most accurate is the variability of breathing pattern descriptors [6]. Central respiratory drive, which is increased during weaning failure, constitutes an alternative approach for predicting weaning. Occlusion pressure (P0.1) and P0.1-derived parameters are among its surrogates [7–12], but the performance of these parameters remains controversial [13]. In addition, although P0.1 is a marker of respiratory drive, it is influenced by muscle strength. This is in contrast to the diaphragm electromyographic activity (EAdi)-derived indices, which have recently become easier to determine with the availability of the neurally adjusted ventilatory assist (NAVA) catheter [14]. Deemed to be used in conjunction with the NAVA mode, which subordinates the ventilator cycle and level of assistance to EAdi, the NAVA catheter consists of a nasogastric feeding tube equipped with a multiple-array esophageal electrode that provides real time access to EAdi.

In the study reported here, we hypothesized that EAdi would provide reliable predictors of weaning success. Our aim was therefore to compare patients successfully separated from the ventilator and the endotracheal tube with those who were not, in terms of various EAdi-derived indices recorded during the SBT. We also compared the performance of these indices to the performance of the RR/V_T. Finally, because it has been demonstrated that indices of breathing variability can discriminate weaning success from weaning failure [6], we also sought to evaluate the indices of EAdi variability to predict weaning success.

Materials and methods

The study was conducted over a 12-month period (1 November 2010 to 1 November 2011) in a ten-bed Intensive Care Unit (ICU) within an 1,800-bed university hospital. The protocol was approved by the institutional review board of the French Learned Society for Intensive Care Medicine (no. 11–321). Informed consent was obtained from the patients.

Patients

Patients intubated and ventilated for at least 24 h were eligible for inclusion in the study if (1) they had been previously mechanically ventilated with NAVA mode and the NAVA catheter had been left in place [the preconditions for NAVA are listed in the Electronic Supplementary Material (ESM)] and (2) they met the predefined readiness-to-wean criteria on the daily screening (see ESM). Patients with neuromuscular diseases and those for whom life support would be withheld or withdrawn were not included in the study.

Spontaneous breathing trial protocol

As soon as the patients fulfilled the readiness-to-wean criteria, a 30-min SBT was performed with the patient connected to the ventilator (pressure support level 7 cmH_2O, zero end expiratory pressure). The SBT was considered to be a failure if at least one the following criteria was present: (1) blood oxygen saturation (SpO_2) of <90 % with a fraction of inspired oxygen (FiO_2) of ≥50 %; (2) acute respiratory distress (RR ≥ 40/min, agitation, cyanosis); (3) systolic arterial blood pressure of ≥180 mmHg; (4) cardiac arrhythmias; (5) respiratory acidosis [pH < 7.32 with an arterial carbon dioxide tension ($PaCO_2$) of ≥50 mmHg]. If none of these failure criteria was present, the SBT was considered as successfully completed and the patient was extubated. This decision was taken by the physician in charge of the patient. The patient was reconnected if signs of intolerance (see above) were present. The separation from the ventilator and the endotracheal tube was considered a success when spontaneous breathing could be sustained without any form of ventilatory support at 48 h after extubation. Conversely, cases of failure included patients who failed the SBT and patients requiring reintubation or any form of ventilator support (including non-invasive ventilation for post-extubation acute respiratory failure) during the first 48 h after extubation. Patients were only studied once, at the first SBT.

Data acquisition

Diaphragm electromyographic activity (obtained from the NAVA catheter; see ESM for detailed EAdi signal processing), airway pressure and flow were acquired at 100 Hz from the ventilator via a RS232 interface connected to a computer using commercially available software (Servo-I® RCR ver. 3.6.2; Maquet Critical Care, Solna, Sweden). Physiologic variables were measured at baseline and at 3, 10, 20 and 30 min during the SBT. Arterial blood gases were sampled at the end of the SBT.

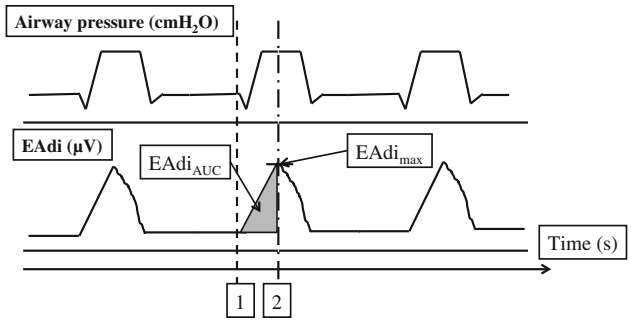

Fig. 1 Schematic representation of the airways pressures and diaphragm electromyographic activity (*EAdi*) signals. *Upper panel* Airway pressure recording, *lower panel* EAdi recording. *Dotted line no. 1* indicates the start of the rise of the EAdi signal, *dashed line no. 2* shows the peak of the EAdi ($EAdi_{max}$). *Grey area* represents the area under the curve of EAdi ($EAdi_{AUC}$)

Data analysis

Respiratory rate (RR), tidal volume (V_T), maximum EAdi ($EAdi_{max}$) and the area under the curve of the EAdi during inspiratory time ($EAdi_{AUC}$, integrated from baseline to peak; Fig. 1) were calculated at the very beginning of the SBT (baseline) and at 3, 10, 20 and 30 min during the SBT. The rapid shallow breathing index (RR/V_T), the $EAdi_{max}/V_T$, the $EAdi_{AUC}/V_T$ and the difference between $EAdi_{max}$ and the lowest EAdi value reported to the V_T ratio ($\Delta EAdi/V_T$) were also computed.

The coefficient of variation (CV), defined as the standard deviation (SD) reported for the mean of both V_T and $EAdi_{max}$, was calculated at 3 and 30 min for a duration of 3 min at each time-point using a software routine developed for Matlab (Mathworks, Natick, MA).

Statistical analysis

The statistical analysis was performed with Prism ver. 4.01 software (GraphPad Software, San Diego, CA). The results are expressed as the median [25–75 % interquartile range (IQR)]. The normality of the distribution was evaluated with the Kolmogorov–Smirnov test. For a given time-point, patients successfully (success group) and unsuccessfully (failure group) separated from the ventilator were compared using Student's *t* test or the Mann–Whitney *U* test as appropriate. Within a given group (success or failure), the five time-points (baseline, 3, 10, 20 and 30 min) were compared using analysis of variance (ANOVA) for repeated measures or the Friedman Test. Categorical variables were compared with the χ^2 test or Fisher's exact test. Differences were considered to be significant when $p < 0.05$. The predictive performance of RR/V_T and EAdi-derived indices at the 3 min time-point was finally assessed with receiver operating characteristic (ROC) curves [15]. For RR/V_T, the cut-off of 100 breaths min^{-1} l^{-1} was retained [3], while for EAdi-derived indices, the cut-off was obtained for each index by determining the better sensitivity and specificity.

Results

Patients's characteristics

A convenience sample of 57 consecutive patients were enrolled in this study (see flow chart in ESM Fig. E1), of whom 35 and 22 patients were successfully and unsuccessfully separated from the ventilator, respectively. In the failure group, the endotracheal tube was not removed at the end of the SBT in 19 patients, and the endotracheal tube was removed but ventilatory support was required within 48 h for three patients. The two groups were similar in terms of demographic and clinical characteristics, but there were more patients with chronic respiratory failure in the failure group (Table 1). Patients in the failure group were longer on mechanical ventilation, but ICU mortality was similar in both groups (Table 1).

Breathing pattern at baseline and during the SBT

At the initiation of the trial, V_T and RR were similar in patients in both groups, but the RR/V_T was higher in patients in the failure group (Table 2). Figure 2 depicts the V_T, RR and RR/V_T at baseline and at 3, 10, 20 and 30 min during the SBT (see also ESM Table E1). During the SBT, RR increased significantly in the failure group and decreased significantly in the success one. Simultaneously, V_T decreased in the failure group, whereas it remained stable in the success group. The RR/V_T ratio did not change over time in the success group, while it increased significantly in the failure group. Overall, 3 min after the beginning of the SBT, V_T, RR and RR/V_T were significantly different between patients who were successfully weaned and those who were not.

EAdi-derived indices at baseline and during the SBT

Table 2 presents the EAdi-derived variables at baseline and Fig. 3 depicts the $EAdi_{max}$, $EAdi_{AUC}$, $EAdi_{max}/V_T$, $EAdi_{AUC}/V_T$ and $\Delta EAdi/V_T$ at baseline and during the SBT at 3, 10, 20 and 30 min (see also ESM Table E1). At the initiation of the trial, all of the EAdi-derived variables were different between patients who were successfully weaned and those who were not (Table 2). These differences remained significant during the entire SBT. However, during the SBT, EAdi-derived variables remained stable throughout the SBT in both the success and failure group with the exception of $EAdi_{max}/V_T$ and $\Delta EAdi/V_T$, which increased significantly in the failure group (Fig. 3).

Table 1 Patients' characteristics

Characteristics	Success group ($n = 35$)	Failure group ($n = 22$)	p
Age (years)	59 (52–72)	67 (58–77)	0.08
Male, *n* (%)	22 (63)	11 (50)	NS
Body mass index (kg m^{-2})	25 (21–27)	28 (21–36)	NS
SAPS II	67 (54–78)	66 (48–79)	NS
Past history, *n* (%)			
Respiratory disease	7 (20)	10 (45)	0.04
Cardiovascular disease	10 (28)	5 (23)	NS
Reasons for initiating mechanical ventilation, *n* (%)[a]			
Acute on chronic respiratory failure	2 (5)	6 (30)	0.06
Community-acquired pneumonia	6 (17)	6 (27)	NS
Cardiogenic pulmonary oedema	6 (17)	5 (23)	NS
Extrapulmonary septic shock	7 (19)	1 (5)	NS
Coma	8 (22)	3 (15)	NS
Post-operative acute respiratory failure	3 (8)	0 (0)	NS
Others	3 (8)	1 (5)	NS
Duration of mechanical ventilation prior to the SBT (days)	2 (1–4)	4 (2–6)	NS
Total duration of mechanical ventilation (days)	2.5 (1.0–4)	6 (4–11)	0.02
ICU mortality, *n* (%)	5 (14)	3 (14)	NS

Unless specified otherwise, data are expressed as the median, with the interquartile range (IQR) given in parenthesis
Success Patients successfully separated from ventilator, *Failure* patients who were unsuccessfully separated from the ventilator, *SAPS* simplified acute physiologic score, *ICU* intensive care unit, *SBT* spontaneous breathing trial, *NS* not significant
[a] Several reasons could justify the mechanical ventilation for the same patient

Table 2 Breathing pattern and diaphragm electromyographic activity-derived indices at baseline

Breathing pattern and EAdi-derived indices at baseline	Success group ($n = 35$)	Failure group ($n = 22$)	p
RR (breaths min^{-1})	29 (23–35)	31 (26–38)	NS
V_T (ml kg^{-1} IBW)	6.1 (5.4–7.5)	5.9 (4.5–6.6)	0.07
RR/V_T (breaths $min^{-1}.l^{-1}$)	60 (42–90)	100 (74–123)	<0.01
$EAdi_{max}$ (μV)	10 (5–18)	17 (9–28)	0.02
$EAdi_{AUC}$ (μV^2)	4 (2–7)	7 (3–11)	0.04
$EAdi_{AUC}/V_T$ ($\mu V^2\ l^{-1}$)	10 (5–16)	19 (10–33)	<0.01
$EAdi_{max}/V_T$ (μV l^{-1})	22 (13–49)	50 (28–106)	<0.01
ΔEAdi/VV_T (μV l^{-1})	20 (10–40)	44 (23–99)	<0.01

Data are expressed as the median, with the IQR given in parenthesis *EAdi* Diaphragm electromyographic activity, *RR* respiratory rate, V_T tidal volume, $EAdi_{max}$ peak of the EAdi, $EAdi_{AUC}$ area under the curve of the EAdi during inspiratory time, *ΔEAdi* difference between $EAdi_{max}$ and the lowest EAdi value

Performance of RR/V_T and EAdi-derived indices at 3 min into the SBT

Figure 4 presents the ROC curves and performance of the RR/V_T (threshold of 100 breaths $min^{-1}\ l^{-1}$), $EAdi_{max}/V_T$, $EAdi_{AUC}/V_T$ and ΔEAdi/V_T at 3 min into the SBT. The best values of sensibility, specificity and AUC were obtained with a threshold of 28 μV l^{-1} for $EAdi_{max}/V_T$, 11 $\mu V^2\ l^{-1}$ for $EAdi_{AUC}/V_T$ and 26 μV $L^{-1}$for ΔEAdi/V_T. The sensitivity and the specificity of these two indices were similar to the performance of RR/V_T.

Variability of the V_T and the $EAdi_{max}$

The CV of the V_T at the onset of SBT was similar in both the success and failure patients [18 (IQR 13–28) vs. 17 (IQR 11–34) %, respectively]. This decreased significantly in both groups during the SBT to reach, by the end of the SBT, 12 (IQR 8–25) % in the success group patients and 12 (IQR 9–21) % in the failure group patients. The CV of $EAdi_{max}$ was also similar in both groups at onset of SBT [success group: 30 (IQR 24–43) %; failure group: 27 (IQR 18–36) %]. However, while the CV of $EAdi_{max}$ decreased during the SBT in success group patients [18 (IQR 9–32) %], it remained unchanged in failure patients [27 (IQR 18–36) %].

Tolerance of the SBT

By the end of the SBT, patients of the failure group had a higher systolic blood pressure, a lower pH and a higher $PaCO_2$ (see ESM Table E2).

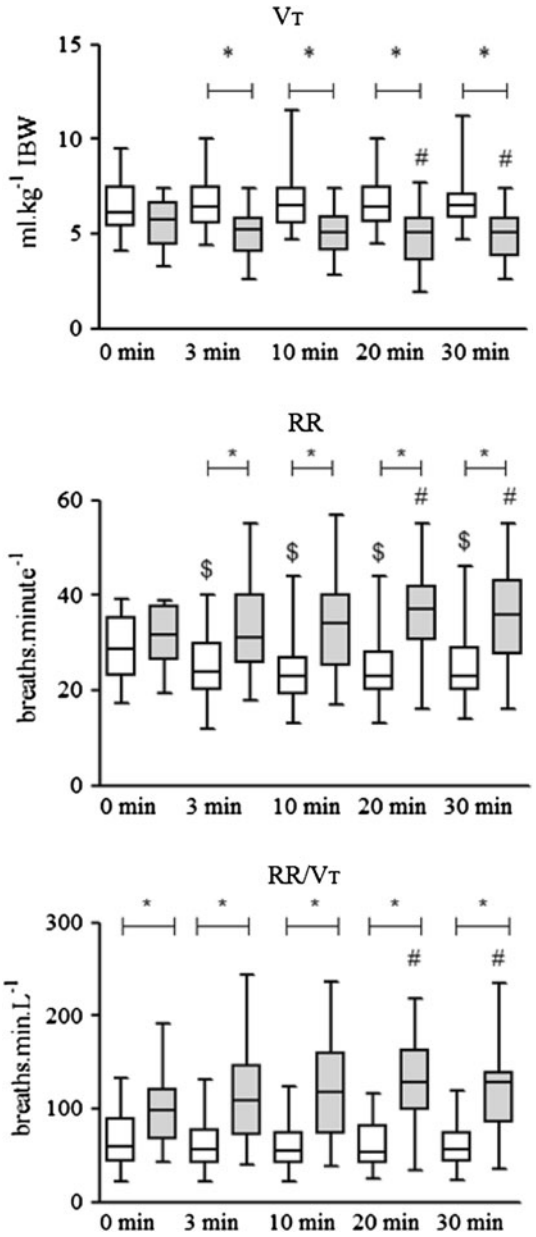

Fig. 2 Breathing pattern during the spontaneous breathing trial (SBT). Tidal volume (V_T) (*upper panel*), respiratory rate (*RR*) (*middle panel*) and RR/V_T ratio (*lower panel*) at baseline and during the SBT (3, 10, 20 and 30 min) in patients successfully separated from the ventilator (*white boxes*; success group) and those who were not (*grey boxes*; failure group). *Line inside the boxes* median, *limits of the boxes* 75th and 25th percentile of the data (interquartile range), *whiskers* minimum to maximum. *$p < 0.05$ vs. failure group, #$p < 0.05$ vs. baseline within the failure group, \$$p < 0.05$ within the success group

Discussion

To our knowledge, this study is the first to report a direct and physiologic approach with NAVA of neuromechanical coupling during the weaning of mechanical ventilation. Our major findings can be summarized as follows: (1) several of the EAdi-derived indices measured during the SBT were significantly different between patients successfully separated from the ventilator and those for whom separation failed; (2) these differences occurred early during the SBT and were even present at baseline; (3) 3 min after the beginning of the SBT, the performance of EAdi-derived indices of neuromechanical coupling was similar to—but not better than—the performance of the RR/V_T ratio; (4) variability of the EAdi signal is not a reliable predictor of weaning failure.

Breathing pattern and EAdi-derived indices during SBT

During the SBT, we observed what has previously been widely described: an increase in the RR with a concomitant decrease in the the V_T in the failure group and no change in the success group [16, 17]. These changes resulted in the development of a rapid shallow breathing pattern in patients who failed the SBT, as suggested by the increased RR/V_T ratio. The RR/V_T ratio was not used as a SBT failure criterion because it might certainly have caused a bias in its comparison with the EAdi-derived indices.

Interestingly, $EAdi_{max}$ and $EAdi_{AUC}$ were higher in the failure than in the success group from the very beginning of the SBT, suggesting that patients who fail the SBT may have a higher respiratory drive at baseline [16]. However, the EAdi did not change significantly during the course of the SBT in either group. This latter observation suggests that the central respiratory drive to the diaphragm did not increase in failure group patients despite these patients developing a rapid shallow breathing. Taken together, these data suggest that during weaning failure, extradiaphragmatic inspiratory muscles, such as sternomastoid and ribcage muscles, are proportionally more recruited than the diaphragm. This suggestion is consistent with the well-observed preferential recruitment of extradiaphragmatic inspiratory muscle during loaded breathing [18]. Hence, EAdi might not be the best surrogate of inspiratory muscles failure during weaning. Of course, the steady EAdi concomitant with the development of a rapid shallow breathing strongly suggests an altered neuro-mechanical coupling.

Beyond ventilatory drive, neuro-mechanical coupling as a marker of weaning failure

We computed various indices of neuro-mechanical coupling, namely $EAdi_{max}/V_T$, $EAdi_{AUC}/V_T$ and $\Delta EAdi/V_T$. These indices reflect the ability of the diaphragm to convert respiratory drive into ventilation. We showed that patients in the weaning failure group had a severe impairment of the neuromechanical coupling of the

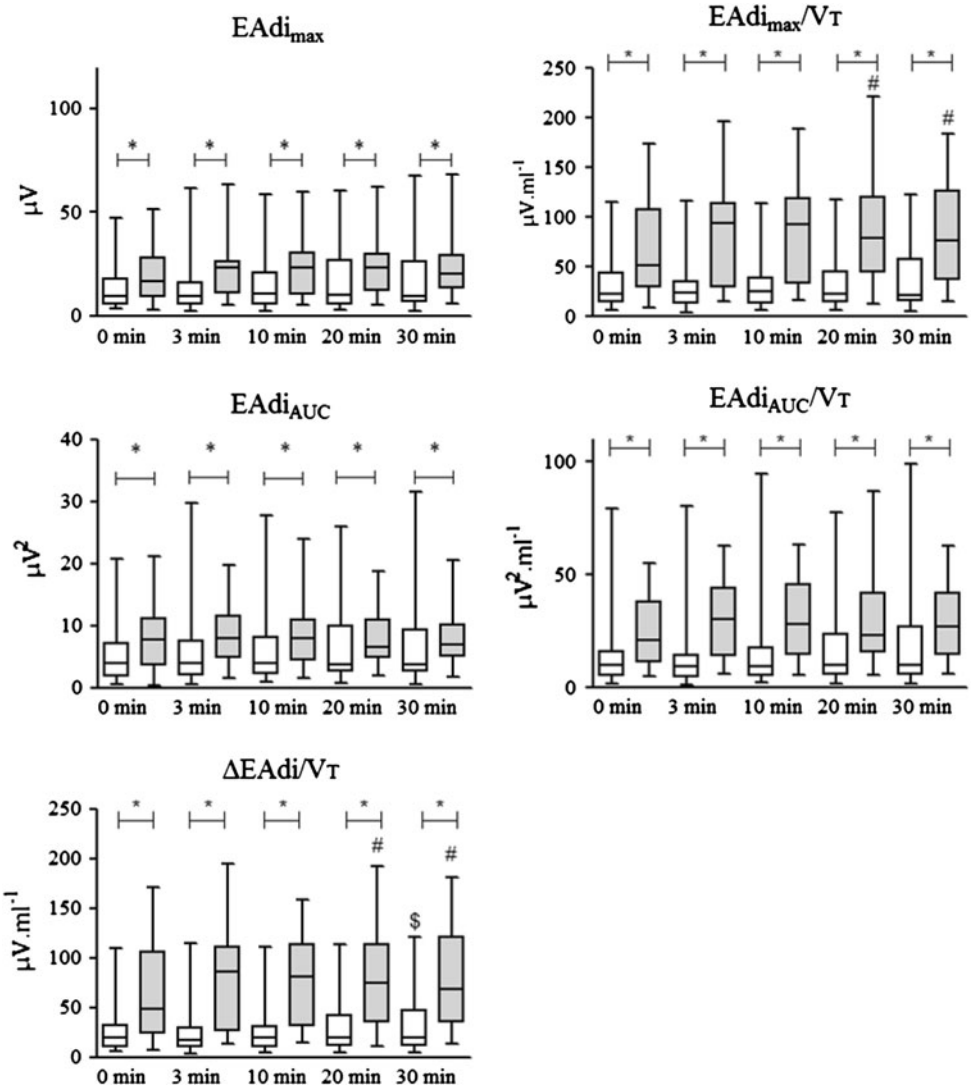

Fig. 3 Diaphragm electromyogaphic activity-derived indices during the SBT. EAdi$_{max}$ (*upper left panel*), EAdi$_{AUC}$ (*middle left panel*), amplitude between the maximal and lowest EAdi ($\Delta EAdi/V_T$) ratio (*lower left panel*), EAdi$_{max}/V_T$ ratio (*right upper panel*) and the EAdi$_{AUC}/V_T$ ratio (*middle right panel*) at baseline and during the SBT (3, 10, 20 and 30 min) in patients successfully separated from the ventilator (*white box*) and those who were not (*grey box*). *Line inside the boxes* Median, *limits of the boxes* 75th and 25th percentile of the data (IQR), *whiskers* minimum to maximum. $^{*}p < 0.05$ versus failure group, $^{\#}p < 0.05$ versus baseline within the failure group, $^{\$}p < 0.05$ within the success group

diaphragm, which was not only present from the beginning of the SBT, but also increased progressively during the entire SBT. All of these indices were able to efficiently discriminate success from failure patients as early as 3 min after the beginning of the SBT. However, the performance of these indices was not superior to the performance of RR/V_T. The fact that the SBT was performed with a pressure support of 7 cmH_2O may have lowered the performance of EAdi-derived indices to discriminate patients who were successful in the SBT from those who failed as 7 cmH_2O of pressure support lowers the performance of the RR/V_T. Indeed, even if the good performance of RR/V_T is well demonstrated while the patient is disconnected from the ventilator and breaths room air without pressure support [2], this is not the case under pressure support [19, 20].

Our results differ slightly from those of Wolf et al. [21] who recently observed in children that the V_T/ΔEAdi ratio after 1 h of SBT decreased dramatically in patients who were successfully weaned while it remained unchanged in those who were not. The different duration of the SBT (1 h vs. 30 min) and the different age of the population (children have indeed a lower rib cage compliance than adults) may explain this discrepancy.

Variability of EAdi

Variability in the various descriptors of the breathing pattern has been shown to be reliably predict weaning success [6]. We therefore sought to evaluate the performance of EAdi variability to predict weaning failure. First, we did not observe an earlier described difference in the CV of the V_T between patients who were successfully separated from the ventilator and those who were not [6]. This is not highly surprising since we performed SBT

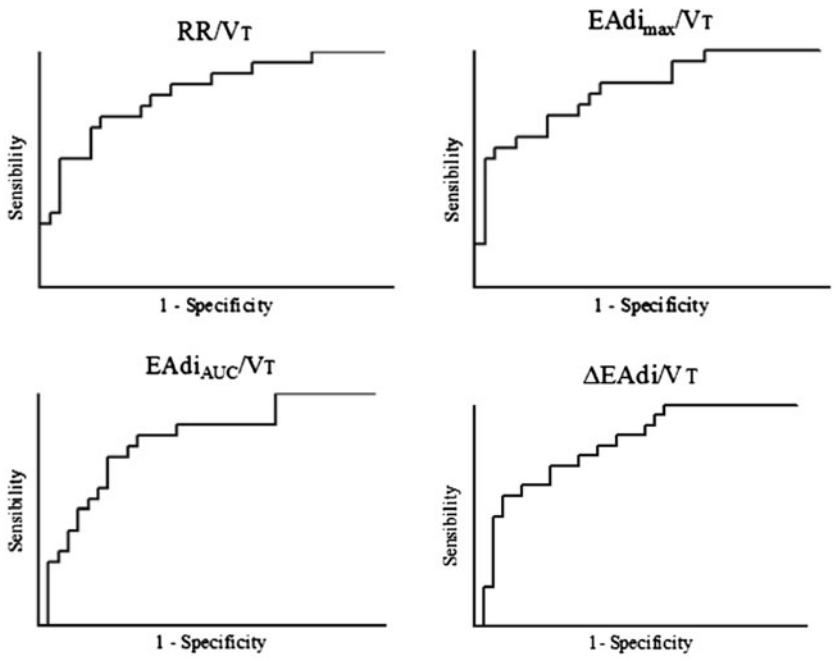

Fig. 4 Receiving operating curves (ROC) for breathing pattern and EAdi-derived indices during the SBT. ROC curves for the RR/V_T ratio (*upper left panel*), $EAdi_{max}$)/V_T ratio (*upper right panel*), $EAdi_{AUC}/V_T$ ratio (*lower left panel*) and $\Delta EAdi/V_T$ ratio (*lower right panel*) to predict the success or failure of the separation of patients from the ventilator at 3 into the SBT. Threshold, sensibility, specificity and area under the ROC curve (AUC) are provided in the *table*

	Threshold	Sensibility	Specificity	AUC
RR/VT	100	60	86	0.83
$EAdi_{max}/VT$	28	77	71	0.84
$EAdi_{AUC}/VT$	11	82	63	0.80
ΔEAdi/VT	26	73	69	0.82

with pressure support and not while the patient was disconnected from the ventilator [22]. Pressure support indeed unloads the respiratory system and therefore alters the load capacity balance of the respiratory system, of which the breathing pattern variability is a surrogate [23]. Secondly, the variability of the EAdi was similar among patients who succeeded and those who failed the SBT. This result is consistent with the findings of a previous study conducted by our group, which showed that the underlying variations in central respiratory neural output activity seem not to be particularly sensitive to the mechanical load [24].

Study limitations

Our study has several limitations. First, it was a single-centre study with a relatively small sample size. Second, to keep the study observational, we only included patients who had been previously ventilated in NAVA, which constitutes a selection bias. Indeed, in our unit, NAVA is given to patients with a poorer tolerance for pressure support ventilation and a longer duration of mechanical ventilation; these patients are eventually more likely to be difficult to wean. In addition, we restricted the study to patients ventilated for more than 24 h, which could explain why chronic obstructive pulmonary disease (COPD) patients were overrepresented in our patient cohort. Third, the SBT was performed with a minimal pressure support of 7 cmH_2O and not with the patient disconnected from the ventilator and breathing room air without pressure support. Compared to a SBT without pressure support ("T-piece"), pressure support ventilation with or without positive end-expiratory pressure (PEEP) is known to markedly modify the breathing pattern and inspiratory muscle effort [20, 25]. Hence, the performance of EAdi-derived indices might have been higher during a SBT performed with a T-piece or PEEP without pressure support. However, in our unit and for safety reasons, the standard of care is to perform the SBT with the patients connected to the ventilator. Because we wished to perform a "real life" study, we did not change the SBT procedure standardly used at our hospital [1]. Fourth, there were more COPD patients in the failure group than in the

success group. In these patients, dynamic hyperinflation may have altered neuromechanical coupling and diaphragmatic performance [26–28]. Moreover, patients with chronic respiratory diseases are known to strongly recruit their extradiaphragmatic inspiratory muscles when facing increased inspiratory load [29]. Fifth, the NAVA catheter has been designed to trigger and adjust ventilatory assist and not for weaning. Thus, it cannot provide information, such as the ratio of high to low frequencies of the electromyograph (H/L), which predicts diaphragm fatigue or excessive loading [30, 31]. Moreover, although we have some information, we do not know the whole signal processing of the technique and have unfortunately no access to raw data. In addition, there might be an inter-subject variability in EAdi recording, depending on many factors and, to date, there is no study that has compared EAdi in large populations of patients. Finally, the study was not strictly blinded. Indeed, the physician in charge of the patients could see the EAdi recordings during the SBT, which may have influenced his/her decision regarding extubation. For this reason, we used strict criteria of SBT success and failure, which are actually those used in our ICU in daily clinical practice. Of note, we did not consider RR/V_T as a criterion for extubation despite its good performance as an index of SBT success or failure as this would have biased the comparison of the performance of this index to the performance of EAdi-derived indices.

Conclusions

EAdi-derived indices collected via the NAVA catheter during the SBT provide reliable predictors of successful separation from the ventilator. These indices can discriminate early in the SBT the ongoing success or failure of separation from the ventilator. However, the performance of these indices is not better than the performance of the rapid shallow breathing index. Therefore, the benefit of EAdi-derived indices during the SBT remains unclear.

Conflicts of interest The Association pour le Développement et l'Organisation de la Recherche en Pneumologie et sur le sommeil, a non-profit structure that supports the research activities of the "Service de Pneumologie et Réanimation Médicale, Groupe Hospitalier Pitié-Salpêtrière", has received an unrestricted research grant from Maquet France SA, Orléans, France, to support pathophysiological research studies on NAVA.

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Electronic Supplement Material

Material and methods

The study was conducted over a twelve months period (November 1, 2010 to November 1, 2011) in a 10-bed Intensive Care Unit (ICU) within an 1800-bed university hospital. The protocol was approved by the institutional review board of the French Learned Society for Intensive Care Medicine (n. 11-321). Informed consent was obtained from the patients.

Patients.

Patients initially intubated and ventilated in the ICU were eligible for inclusion in the study if: 1) They had previously been mechanically ventilated with NAVA mode and the NAVA catheter had been left in place; 2) Sedations had been stopped more than 12 hours previously. The final decision to institute NAVA depended on the physician in charge of the patient who was not involved in the research. However, in our practice, preconditions for the institution of NAVA usually included 1) poor clinical tolerance of PSV for at least 2h when adjusted to provide a tidal volume of 6-8 ml/kg at a setting not exceeding 20 cmH_2O; this was decided by the clinician in charge of the patient, either as a result of a direct indication by the patient that his or her breathing was a matter of discomfort or according to usual clinical criteria; 2) a Ramsay sedation scale score less than 4; 3) FiO_2 less than or equal to 50% and positive end-expiratory pressure less than or equal to 10 cm H_20; 4) hemodynamic stability without vasopressor or inotropic medication; 5) estimated remaining duration of mechanical ventilation more than 48h. The exclusion criteria for using NAVA mode in invasive ventilation were mainly related to contra-indications to the use of NAVA: known or suspected phrenic nerve dysfunction impaired respiratory drive, neuromuscular disease, and

contraindications to EAdi catheter placement (e.g., esophageal varices or obstruction, recent gastroesophageal surgery, facial surgery or trauma, or upper gastrointestinal bleeding).

During the study period, 610 patients were hospitalized in our unit. Among them, 295 patients received invasive ventilation of which 265 were eventually mechanically ventilated for more than 24 hours. Among these 265 patients, 75 patients were equipped with a NAVA probe thus eligible. Were eventually not included in the study the 10 patients who failed to be screened and 8 patients who died before inclusion. Hence, the study pertained to a convenience sample of 57 consecutive patients (see figure E1).

Predefined readiness to wean criteria

Resolution of disease acute phase for which the patient had received invasive mechanical ventilation, adequate cough, adequate oxygenation defined by $SpO_2 > 90\%$ with $FiO_2 \leq 50\%$, respiratory rate $\leq$ 40 breathes min^{-1}, a Ramsay sedation scale score less than 4; and stable cardiovascular status (heart rate $\leq$120 $beats.min^{-1}$, systolic arterial blood pressure $\leq$180 mmHg and no or minimal vasopressors (norepinephrine <5 μg/Kg/min).

Ventilator

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

Spontaneous breathing trial protocol

As soon as the patients fulfilled the readiness-to-wean criteria, the position of the EAdi NAVA catheter (size, 16 Fr) was checked according to the manufacturer's recommendations [1] and a 30 minutes SBT was performed with the patient connected to the ventilator with a pressure support level of 7 cmH_2O and zero end expiratory pressure. The SBT was considered as a failure if at least one the following criteria was present: 1) $SpO_2 < 90\%$ with $FiO_2 \geq 50\%$, 2) acute respiratory distress (RR $\geq$ 40/min, agitation, cyanosis), 3) systolic arterial blood pressure $\geq$ 180 mmHg, 4) suddent cardiac arrhythmias, and 5) respiratory acidosis (pH < 7.32

with $PaCO_2 \geq 50$ mmHg. If none of the above failure criteria was present, the SBT was considered as successfully completed and the patient was extubated. This decision was taken by the physician in charge of the patient. The patient was reconnected if signs of intolerance (see above) were present. The separation from the ventilator and the endotracheal tube was considered a success when spontaneous breathing could be sustained without any form of ventilatory support with 48 hours after extubation. Conversely, cases of failure included patients who failed the SBT and patients requiring reintubation or any form of ventilator support (including non invasive ventilation for post extubation acute respiratory failure) during the 48 hours after extubation. Patients were only studied once, at the first SBT.

Data Acquisition

EAdi was obtained from the NAVA catheter. This esophageal catheter collects the diaphragmatic electromyographic signal with bipolar electrodes in a sequential order. An automated processing technique tracks the displacement of the diaphragm [2]. A cross-correlation technique (for every second pair of electrodes) determines every 16 milliseconds the position of the diaphragm along the array. Subtraction of opposite phase signals above and below the diaphragm results in a new signal: the "double-subtracted" signal. This double-substracted signal is free from distance filtering. In addition, signal-to-noise ratio is enhanced [2]. The root-mean-square (RMS) of this signal is then calculated every 16 milliseconds, and added to the RMS of the center signal (i.e., from the electrode pair closest to the muscle) [3, 4]. The resultant RMS values for every 16 milliseconds sample can be graphically connected, resulting in the EAdi waveform [5]. The RMS is linearly related to the number of motor units recruited and their firing rate. Finally, the electrocardiographic signal is detected and replaced by a value predicted from the previous Edi value. To further reduce electrical noise disturbances (e.g., 50 or 60 Hz) and motion artefacts and to minimize electrocardiographic and electrical activity from the oesophagus, the signal is eventually filtered with a cascade of filters.

EAdi, airway pressure and flow were acquired at 100 Hz from the ventilator via a RS232 interface connected to a computer using commercially available software (Servo-i® RCR, version 3.6.2, Maquet Critical Care).

Physiologic variables (heart rate, systolic arterial blood pressure and SpO_2) were measured at baseline, 3, 10, 20 and 30 minutes. Arterial blood gases were sampled at the end of the SBT.

Data analysis

Respiratory rate (RR), tidal volume (V_T), maximum EAdi ($EAdi_{max}$) and the area under the curve of the EAdi during inspiratory time ($EAdi_{AUC}$), were calculated at the very beginning of the SBT (baseline) and at 3, 10, 20 and 30 minutes. The $EAdi_{AUC}$ was calculated as the integration of the EAdi signal between the start of the rise of EAdi from baseline and the peak of the curve (figure 4). The rapid shallow breathing index (RR/V_T), the $EAdi_{max}/V_T$, the $EAdi_{AUC}/V_T$ and the difference between $EAdi_{max}$ and the lowest EAdi value reported to the V_T ratio ($\Delta EAdi/V_T$) were also computed.

The coefficient of variation, defined as standard deviation reported to the mean of both V_T and $EAdi_{max}$, was calculated at 3 and 30 minutes over a 3 minute period using a software routine developed for Matlab (Mathworks, Natick, MA).

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Table E1. Breathing pattern and diaphragm electromyographic activity (EAdi)-derived indices during the spontaneous breathing trial

		Baseline	3 minutes	10 minutes	20 minutes	30 minutes
RR, *breaths.min^{-1}*	Success	29 (23-35)	24 (20-30)$^{\$*}$	23 (19-27)$^{\$*}$	23 (20-28)$^{\$*}$	23 (20-29)$^{\$*}$
	Failure	31 (26-38)	31 (26-40)	34 (25-40)	36 (29-42)$^{\#}$	35 (26-43)$^{\#}$
V_T, *ml.kg^{-1} IBW*	Success	6.1 (5.4-7.5)	6.4 (5.5-7.5)*	6.5 (5.5-7.4)*	6.4 (5.6-7.5)*	6.5 (5.8-7.1)*
	Failure	5.9 (4.5-6.6)	5.3 (4.0-5.9)	5.2 (4.0-5.9)	5.1 (3.6-5.8)$^{\#}$	5.1 (3.8-5.8)$^{\#}$
RR/V_T, *breaths.min^{-1}.l^{-1}*	Success	60 (42-90)*	56 (42-78)*	55 (41-74)*	54 (42-82)*	57 (42-74)*
	Failure	100 (74-123)	109 (77-147)	118 (80-163)	131 (99-167)$^{\#}$	130 (85-158)$^{\#}$
$EAdi_{max}$, μV	Success	10 (5-18)*	9 (5-16)*	10 (5-16)*	9 (5-24)*	9 (6-26)*
	Failure	17 (9-28)	23 (11-28)	23 (10-30)	23 (13-30)	20 (13-29)
$EAdi_{AUC}$, μV^2	Success	4 (2-7)*	4 (2-7)*	4 (2-8)*	4 (3-10)*	4 (3-9)*
	Failure	7 (3-11)	8 (5-11)	7 (4-11)	7 (5-11)	7 (5-10)
$EAdi_{AUC}/V_T$, $\mu V^2.l^{-1}$	Success	10 (5-16)*	9 (4-14)*	9 (5-17)*	10 (5-23)*	9 (5-27)*
	Failure	19 (10-33)	29 (14-44)	27 (14-45)	23 (15-41)	27 (14-41)
$EAdi_{max}/V_T$, $\mu V.l^{-1}$	Success	22 (13-49)*	24 (13-36)*	24 (13-44)*	22 (13-50)*	22 (16-58)*
	Failure	50 (28-106)	92 (28-113)	92 (32-118)	80 (43-119)$^{\#}$	76 (36-125)$^{\#}$
$\Delta EAdi/V_T$, $\mu V.l^{-1}$	Success	20 (10-40)*	18 (9-32)*	21 (10-42)*	20 (11-48)*	21 (11-53)$^{*\$}$
	Failure	44 (23-99)	83 (26-106)	81 (30-114)	74 (35-114)$^{\#}$	69 (35-121)$^{\#}$

Success, patients successfully separated from ventilator; *Failure*, patients who failed separation from the ventilator; *RR*, Respiratory Rate; *V_T*, Tidal Volume; *$EAdi_{max}$*, Peak of the EAdi; *$EAdi_{AUC}$*, area under the curve of the EAdi during inspiratory time; *$\Delta EAdi$*, difference between $EAdi_{max}$ and the lowest EAdi value; *IBW*, Ideal Body Weight.

* $p<0.05$ versus failure groups. # $p<0.05$ versus baseline within the failure group. $ $p<0.05$ versus baseline within the success group.

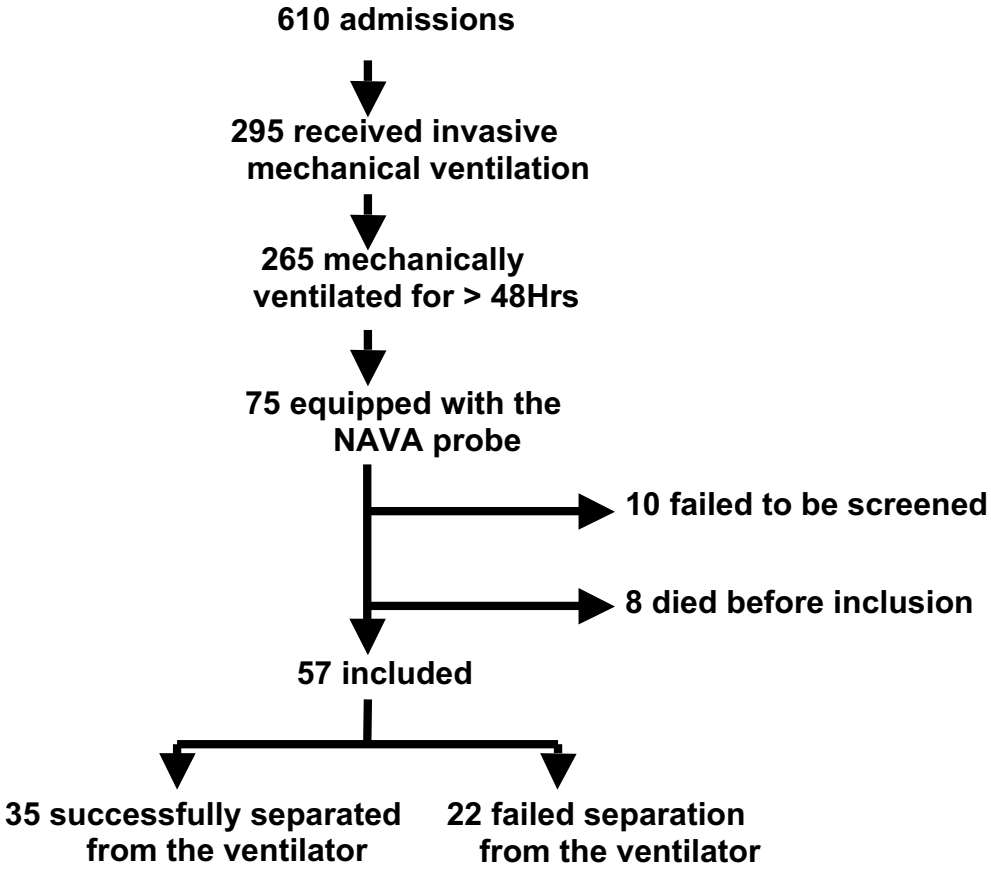
Data are expressed as median (interquartile range).

Table E2. Physiological variables and blood gas

	Success (n=35)	Failure (n=22)
Beginning of the SBT		
Heart rate, *bpm*	98 (86-108)	91 (78-104)
Systolic arterial pressure, *mmHg*	124 (108-145)	138 (122-149)
Diastolic arterial pressure , *mmHg*	62 (55-76)	64 (59-78)
Pulse Oxygen Saturation, *%*	97 (94-100)	97 (95-100)
End of the SBT		
Heart rate, *bpm*	97 (86-108)	96 (86-110)
Systolic arterial pressure, *mmHg*	124 (110-152)	146 (130-168)*
Diastolic arterial pressure , *mmHg*	62 (55-76)	69 (62-77)
Pulse Oxygen Saturation, *%*	97 (94-100)	97 (91-99)
Arterial blood gas at the end of the SBT		
PaO_2,*mm Hg*	78 (68-106)	74 (61-103)
$PaCO_2$,*mm Hg*	35 (32-40)	45 (38-66)*
pH	7.44 (7.40-7.51)	7.39 (7.30-7.44)*
HCO^{3-}, *mEq/L*	25 (22-26)	31 (25-34)*

Success, patients successfully separated from ventilator; *Failure,* patients who failed separation from the ventilator; *SBT*, spontaneous breathing trial.
* $p<0.05$ *versus* success group

Figure E1: Flow chart of the study



Diaphragm function and liberation from mechanical ventilation: An ultrasound and phrenic nerve stimulation clinical study

Martin Dres[1,2], MD, Ewan C. Goligher[3,4], MD, PhD, Bruno-Pierre Dubé[1,5], MD, Elise Morawiec[2], MD, Laurence Dangers[1,2], MD, PhD, Danielle Reuter[2], MD, Julien Mayaux[2], MD, Thomas Similowski[1,2], MD, PhD and Alexandre Demoule[1,2], MD, PhD

[1]Sorbonne Universités, UPMC Univ Paris 06, INSERM, UMRS1158 Neurophysiologie respiratoire expérimentale et clinique, Paris, France

[2]AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie et Réanimation Médicale (*Département "R3S"*), F-75013, Paris, France

[3]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada

[4]Department of Medicine, Division of Respirology, University Health Network and Mount Sinai Hospital, Toronto, Canada

[5]Département de médecine, service de pneumologie, hôpital Hôtel-Dieu, Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, Québec, Canada

Correspondence:
Dr Martin Dres
Service de Pneumologie et Réanimation Médicale, Groupe Hospitalier Pitié-Salpêtrière
47-83 boulevard de l'Hôpital, 75651 Paris Cedex 13, France
Phone: 33 1 42 16 77 61; Fax: 33 1 70 24 72 82
E-mail: martin.dres@aphp.fr

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Competing interests

Alexandre Demoule has signed research contracts with Covidien, Maquet and Philips; he has also received personal fees from Covidien, Maquet, Resmed, Fisher & Paykel and MSD. Martin Dres received personal fees from Pulsion Medical System and AstraZeneca. Bruno-Pierre Dubé has received honoraria from GlaxoSmithKline, Boehringer Ingelheim, Astra Zeneca and Roche. Relevant to the present study, Thomas Similowski has received personal fees from Lungpacer Inc and is a member of the board of a research association that has received, over the past ten years, unrestricted research grants from Maquet, Hamilton, Covidien, and Philips; he is the head of a research unit (UMRS 1158) that has signed research contracts with Air Liquide Medical Systems, France; he is listed as inventor or co-inventor on several patents, granted or pending, describing a brain-ventilator interface. The others authors have no conflict of interest relevant to this study.

Abstract (252 words)

Background: Diaphragm dysfunction is defined by a value of twitch tracheal pressure in response to magnetic phrenic stimulation (twitch pressure) amounting to less than 11 cmH_2O. The present study assessed whether this threshold or a lower one would predict with accuracy successful liberation from mechanical ventilation. Twitch pressure was compared to different measures of diaphragm function.

Methods: In patients undergoing a first weaning trial, diaphragm function was evaluated by twitch pressure and by diaphragm ultrasound (thickening fraction). The rapid shallow breathing index was also calculated. Receiver operating characteristics curves were computed to determine the best thresholds predicting successful liberation (successful weaning trial followed by extubation without re-institution of ventilation within 48 hours).

Results. 76 patients were evaluated (57 in a development cohort and 19 in a validation cohort). The optimal thresholds of twitch pressure, thickening fraction and rapid shallow breathing index to predict successful liberation were respectively 7.8 cmH_2O, 29%, 50 $breath.min^{-1}.l^{-1}$, respectively. The receiver operating characteristics curves were similar for twitch pressure and thickening fraction, 0.87 (95% confidence interval : 0.75–0.94) and 0.85 (95% confidence interval : 0.73–0.93), respectively) and significantly higher than rapid shallow breathing index (0.69, 95% confidence interval : 0.56–0.81). Validation cohort confirmed the performance of these indices in the prediction of successful liberation from mechanical ventilation.

Conclusions: Successful liberation from mechanical ventilation can be predicted with a lower value of twitch pressure than the value defining diaphragm dysfunction.

Twitch pressure and thickening fraction had similar strong performance in the prediction of successful weaning.

Key Words: diaphragm weakness, extubation, liberation from mechanical ventilation, diaphragm ultrasound, phrenic stimulation.

Introduction

Diaphragm dysfunction is common in critically ill patients exposed to mechanical ventilation. It can occur soon after intubation.[1] It can also occur later, where it may be a consequence of intensive care unit acquired weakness[2] or the result of the specific time-dependent impact of mechanical ventilation on the diaphragm,[2–4] a phenomenon referred to as ventilator induced diaphragm dysfunction.[5] Diaphragm dysfunction is associated with increased mortality [1,2] and delayed liberation from mechanical ventilation.[2–4,6]

Diaphragm dysfunction manifests as a reduced capacity to generate inspiratory pressure and flow.[7] This can be assessed in term of the negative pressure swing measured at the opening of an endotracheal tube in response to bilateral phrenic nerve stimulation (Ptr,stim).[8] Outside of the intensive care context, a Ptr,stim value amounting to less than 11 cmH_2O is considered indicative of diaphragm dysfunction.[1,9–11] In critically ill patients, this value of -11 cmH_2O has proven useful from a prognostic point of view. In a prospective study of ICU patients in whom Ptr,stim was measured at time of weaning, the patients with a Ptr,stim below the 11 cmH_2O threshold were less likely to survive to discharge from the ICU or hospital than those with a Ptr,stim above this threshold.[2] Yet, lower Ptr,stim values are commonly encountered in ICU patients at various points of their ICU stay[1,2,4,8] and two recent studies have reported successful liberation from mechanical ventilation despite lower values of Ptr,stim.[2,4] Therefore, the Ptr,stim threshold value used to define diaphragm dysfunction (-11 cmH_2O) is not necessarily the best threshold that allows successful liberation from mechanical ventilation. The present study was designed to identify the optimal Ptr,stim value to predict successful liberation from mechanical ventilation. In view of the recently

reported utility of diaphragm thickening fraction (TFdi)[12] to predict successful liberation from mechanical ventilation, the predictive value of this variable was also evaluated. Ptr,stim and TFdi were compared to the rapid shallow breathing index (RSBI), a widely-employed predictor of weaning outcome[13].

Patients and methods

The study was prospectively conducted over 9 months (November 1, 2014 to July 31st, 2015) in a medical ICU. The study was approved by the Comité de Protection des Personnes Ile-de-France VI (ID RCB: 2014-A00715-42). Informed consent was obtained from all patients or their relatives. Data from this cohort have been previously published.[2,14]

Patients

Patients were eligible for inclusion in the study if they had been intubated and ventilated for at least 24 hours and if they met predefined readiness-to-wean criteria on daily screening[15] and were therefore ready for a first trial of spontaneous breathing (see details in the Supplemental Digital Content). Patients with clinical factors potentially interfering with phrenic nerve stimulation, who had a tracheostomy, or who were unable to follow simple orders were excluded.

Measurements

Measurement techniques are described in detail in the Supplemental Digital Content. All measurements were performed immediately before starting the spontaneous breathing trial (SBT). Phrenic nerve stimulation was performed while patients were briefly disconnected from the ventilator; diaphragm ultrasound measurements and the RSBI were obtained while patients were mechanically ventilated with a pressure-support level providing a tidal volume of 6-8 ml/kg of ideal body weight and without signs of labored breathing, as defined by retractions or recessions - sucking in of the skin around the ribs and the top of the sternum, or prominent use of accessory respiratory muscles. Positive end-expiratory pressure was set at 5 cmH_2O.

Diaphragm function was assessed in terms of Ptr,stim, as described elsewhere.[8,10] Stimulations were delivered at the maximum intensity allowed by the stimulator (100%) known to result in supramaximal diaphragm contraction in most patients.[1,8,9,16,17] Diaphragm ultrasound was conducted using a 4-12 MHz linear array transducer (Sparq ultrasound system, Phillips, Philips Healthcare, MA, USA) using techniques described elsewhere.[2] Diaphragm thickness was measured at end-expiration (Tdi,ee) and end-inspiration (Tdi,ei) and thickening fraction (TFdi) was calculated offline as (Tdi,ei – Tdi,ee)/Tdi,ee. Sonographers were blinded to the results of phrenic nerve stimulation and RSBI. The reproducibility of these measurements in our research team has been previously reported.[2]

RSBI was calculated as the ratio of respiratory rate over tidal volume while patients were still connected to the ventilator. Ventilator settings were not modified during the measurement. Respiratory rate was obtained by direct examination of the patient for 60 seconds. Tidal volume was derived from minute volume recorded by the ventilator over the same 60-second period. RSBI was computed as respiratory rate over tidal volume. Measurements were not performed in subjects who were coughing, had copious secretions, were recently suctioned, or had a recent change in position. In these last cases, RSBI was re-measured after few minutes of steady-state ventilation. A single measurement was obtained for each patient.

Study design

After obtaining study measurements, patients underwent an SBT. During the SBT, patients were ventilated with a pressure support level 7 cmH_2O and 0 cmH_2O end-expiratory pressure for 30 minutes. Patients were deemed to have failed the SBT if they developed criteria for clinical intolerance (see Supplemental Digital Content). Otherwise, the SBT was considered to be successful and patients were

extubated according to the decision of the attending physician. Successful liberation was defined as a successful SBT followed by extubation and sustained spontaneous breathing without any re-institution of any form of ventilatory support for 48 h after extubation as per international consensus conference on weaning.[15] Patients who received only prophylactic non-invasive ventilation after extubation at their physician's discretion[18] were considered as successfully liberated from mechanical ventilation. Reintubation and use of non-invasive ventilation for post-extubation respiratory distress was permitted according to physician discretion. For patients with failed SBT or who required reintubation, only their first SBT was considered for the analysis.

Statistical analysis

Continuous variables are expressed as median (interquartile range) and categorical variables are expressed as absolute and relative frequency. Continuous variables were compared with Mann-Whitney U test.

The manuscript conforms to the STARD checklist for reporting of studies of diagnostic accuracy.[19] Receiver Operating Characteristic (ROC) curves were constructed to evaluate the performance of the following three indices to predict successful liberation from mechanical ventilation: Ptr,stim, TFdi and RSBI. Sensitivities, specificities, positive and negative predictive values, positive and negative likelihood ratios and areas under the ROC curves (AUC-ROC) were calculated. The best cut-off value for each indice was determined as the value yielding the optimal combination between sensitivity and specificity for the prediction of successful liberation from mechanical ventilation. AUC-ROC were compared using the non-parametric approach of DeLong et al.[20]

An *a posteriori* sample size calculation was made by considering an AUC-

ROC of Ptr,stim higher than 0.80 to predict successful liberation from mechanical ventilation. Accordingly, assuming a prevalence of 60 % of successful liberation, a sample of 38 patients would have been deemed sufficient to demonstrate that Ptr,stim can predict successful liberation with a Type I error rate of 0.05 and a Type II error rate of 0.10 (90 % power). Hence, the predictive performances of the indices were first computed into a development cohort representing two thirds of the whole cohort and the cut-offs of the resulting indices were tested into a validation cohort.

A sensitivity analysis was performed to assess the predictive performance of all indices in the prediction of the outcome of the SBT.

For all final comparisons, a two tailed p-value less than or equal to 0.05 was considered statistically significant. Statistical analyses were performed with MedCalc (MedCalc Software bvba).

Results

Over the study period, 57 patients were included into the development cohort. The characteristics of these 57 patients are given in Table 1. Thirty-two patients (63%) passed the SBT and were successfully liberated while 25 patients (37%) developed failed liberation (see flowchart, Figure 1). Of the patients with failed liberation, 21 failed the SBT and 4 other patients passed the SBT and were subsequently extubated but required resumption of ventilatory support (3 reintubation and 1 curative non invasive ventilation) within 48 hours: three patients for respiratory distress and one patient for loss of consciousness. There was no patient in whom mechanical ventilation was resumed after 48 hours and before day 7. No stridor was reported. Prophylactic non-invasive ventilation was used in two patients successfully liberated from mechanical ventilation.

Prediction of successful liberation from mechanical ventilation

Overall, Ptr,stim was 8.3 (5.7–12.7) cm H2O, 11.0 (8.0–15.0) and 4.5 (3.1–7.6) cmH_2O in patients who were successfully liberated and who failed attempted liberation, respectively ($p<0.001$). The optimal threshold value of Ptr,stim to predict successful liberation was 7.8 cmH2O. Predictive performances of the of Ptr,stim are shown in Table 2. Ptr,stim value greater than 11 cmH_2O (defining diaphragm dysfunction) predicted successful liberation with a sensitivity of 53% (95% CI, 35–71%) and a specificity of 88% (95% CI, 69–97%).

TFdi was 28% (18–35) in the whole population, 33% (26–40) and 18% (10–26) in patients who were successfully liberated and who failed attempted liberation, respectively ($p<0.001$). The optimal threshold value of TFdi to predict successful liberation was 29%. Predictive performances of the TFdi are shown in Table 2.

RSBI was 50 (42–63) breaths.min^{-1}.l^{-1} in the whole population, 46 (37–59) and 53 (46–77) breaths.min^{-1}.l^{-1} in patients who were successfully liberated and who failed attempted liberation, respectively (p=0.01). The optimal threshold value of RSBI to predict successful liberation was 50 breaths.min^{-1}.l^{-1}. Predictive performances of RSBI are shown in Table 2.

Comparison between different indices to predict successful liberation from mechanical ventilation

AUC-ROC of the three indices is shown in Figure 2. Ptr,stim and TFdi had similar AUC-ROC (p=0.64) that were both significantly higher than AUC-ROC of RSBI (p=0.02 and p=0.04, respectively).

Sensitivity analysis looking at the performance of the indices to predict spontaneous breathing trial outcome (success vs. failure)

Thirty-six patients passed and 21 failed the SBT. Sensitivity analysis found slightly lower predictive performances of the three indices to predict SBT success as compared to the prediction of successful of liberation from mechanical ventilation (see Table Supplemental Digital Content 1).

Validation cohort

An additionnal cohort of 19 patients (development cohort) was used to test the validity of the predefined cut-offs. The characteristics of these patients are given in Table 1. Nine patients (47%) passed the SBT and were successfully liberated while 10 patients (53%) developed failed liberation. The predictive performances of Ptr,stim, TFdi and RSBI in the validation cohort are given in Table Supplemental Digital Content 2. The predictive performances of the indices in the validation cohort were similar to the development cohort.

Discussion

This study reports a multimodal assessment of diaphragm function and its relationship with weaning outcome in mechanically ventilated patients undergoing a first spontaneous breathing trial. Our findings can be summarized as follows: 1) a lower value of Ptr,stim (8 cmH_2O) than the value commonly accepted value to define diaphragm dysfunction (11 cmH_2O) is more reliable to predict successful liberation, 2) Ptr,stim and TFdi are equivalent and both superior to RSBI to predict successful liberation from mechanical ventilation.

Diaphragm function and liberation from mechanical ventilation

The negative impact of diaphragm dysfunction on successful liberation from mechanical ventilation has been established by several investigations in critically ill patients.[2–4,6,12] At the time of weaning, diaphragm dysfunction is highly prevalent with reported rates ranging from 25-30%[3,6] to 60-80%.[2,4] To our knowledge, only three studies have assessed diaphragm dysfunction at the time of attempted liberation from mechanical ventilation using the gold standard technique, phrenic nerve stimulation.[2,4,21] However, none of them provided any threshold values for Ptr,stim to predict successful liberation. Of note, these studies including ours indicate that a substantial proportion of patients (up to 44%) can be successfully weaned from the ventilator despite having diaphragm dysfunction defined as Ptr,stim < 11 cmH_2O.[2,4] Therefore, *normal* diaphragm function according to a definition established in healthy subjects[7] is not a prerequisite for successful liberation from mechanical ventilation. This finding is not altogether surprising as many patients with chronic diaphragm weakness do not require mechanical ventilation[22–24] While diaphragm dysfunction might limit exercise capacity, the clinical consequences of diaphragm dysfunction in successfully liberated patients is

uncertain. However, the impact of respiratory muscles dysfunction (not specifically the diaphragm) after critical illness may be of importance since it is associated with worse long-term outcomes.[25,26] Overall, our findings are of importance since they highlight that presence of diaphragm dysfunction at the time of weaning should not discourage clinicians from attempting liberation from ventilation.

Diaphragm ultrasound in the prediction of liberation from mechanical ventilation

The use of diaphragm ultrasound is growing in the ICU.[27] It has many advantages over phrenic nerve stimulation, which requires costly equipment and extensive technical expertise. Ultrasound is a non-invasive and highly feasible bedside imaging modality[28] and ultrasound devices are widely available in ICUs. Several studies have proposed various ultrasound-derived markers aiming at assessing diaphragm function. Three studies investigated diaphragm excursion and compared it to RSBI[3,6,29] and three others investigated diaphragm thickening fraction and compared it to RSBI,[12,30,31]. We found that TFdi was a better predictor than RSBI. Importantly, Ptr,stim and TFdi demonstrated similar performance in the prediction of successful liberation. Of note, the optimal TFdi cut-off (29%) identified in our study is very close to the cut-offs reported in previous investigations.[3,12] Considering ultrasound as a substitute of phrenic nerves stimulation technique, it will make diaphragm evaluation much easier at the bedside. Regarding the performance of RSBI, we report lower performance in the prediction of weaning success as compared to the seminal paper by Yang and Tobin.[13] This finding is likely explained by the method we used: RSBI was measured while patients were ventilated with pressure support and not disconnected from the ventilator.

Strengths and limitations of our study

This study is the largest to report a multimodal approach providing comparison between the gold standard evaluation method of diaphragm function, diaphragm ultrasound and RSBI. However, this study has limitations. First, the generalizability of our findings may be limited by the characteristics of the patients enrolled who were mainly medical patients. Second, we performed diaphragm ultrasound while patients were ventilated with pressure-support and not during the SBT. This method could underestimate diaphragm thickening.[30,32] However, this approach is easier to implement (no change in ventilator setting) and less stressful for patients. We would emphasize that the amount of pressure support was standardized in order to target a tidal volume between 6 and 8 ml/kg predicted body weight. Reassuringly, any effect of ventilatory support on TFdi is likely to introduce 'noise' in its correlation with weaning outcome and this would tend to bias the observed association towards the null. Third, the definition of successful liberation from mechanical ventilation can be questioned since it was defined at 48 hours and not after seven days. The later cut-off may be considered more appropriate to observe the consequences of diaphragm dysfunction. While the 48 hours-cut-off was chosen according to the current international conference consensus on weaning,[15] we also observed that mechanical ventilation was resumed in any patient after 48 hours. Therefore, we concluded that changing the definition would not have modified our findings.

Conclusion

Diaphragm ultrasound is a reliable surrogate of the phrenic nerve stimulation method in the assessment of diaphragm function to predict weaning outcome. A multi-centre investigation is now required to confirm whether the 29% value of

TFdi cut-off could or could not be used widely to predict weaning outcome. Diaphragm ultrasound could be combined with cardiac echo or lung ultrasound to tailor post extubation management according to the risk of weaning failure. Although diaphragm dysfunction did not systematically impair weaning outcome, it may behave as a marker of severity and poor prognosis. Future studies should address this hypothesis and investigate mid- and long-term consequences of diaphragm dysfunction on patient functional status and quality of life.

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Table 1. Patient's characteristics at inclusion

Characteristics	Development cohort	Validation cohort
	N=57	N=19
Female, *n (%)*	15 (26)	9 (52)
Age, *years*	58 (48–68)	53 (50–70)
Body Mass Index, kg/m^2	24 (21–28)	25 (23–27)
SAPS 2	46 (29–59)	34 (16-52)
Duration of mechanical ventilation, *days*	4 (2-6)	4 (2-6)
Reason for mechanical ventilation		
Acute respiratory failure, *n (%)*	21 (37)	10 (53)
Coma, *n (%)*	18 (31)	4 (21)
Shock, *n (%)*	18 (32)	5 (26)
Medical conditions		
COPD, *n (%)*	8 (14)	4 (21)
Chronic liver disease, *n (%)*	12 (21)	2 (10)
Diabetes mellitus, *n (%)*	10 (18)	4 (21)
Chronic left ventricular failure, *n (%)*	9 (16)	3 (16)
Ventilator parameters		
Pressure support level, cmH_2O	10 (8–10)	8 (8–11)
Tidal volume, *ml/kg ideal body weight*	7 (5–8)	7 (6–8)
PEEP, cmH_2O	5 (5–6)	6 (5–6)
FiO_2, *%*	30 (30–40)	40 (30–40)
Clinical parameters		
Respiratory rate, min^{-1}	22 (20–25)	24 (21–28)
Mean arterial pressure, *mmHg*	80 (69–98)	85 (74–96)
Heart rate, min^{-1}	89 (78–100)	91 (80–111)
Arterial blood gases		
pH	7.44 (7.40–7.45)	7.44 (7.43–7.48)
$PaCO_2$, *mmHg*	38 (34–44)	37 (33–46)
PaO_2/FiO_2	279 (214–357)	240 (220–337)

Continuous variables are expressed as median (interquartile range) and categorical variables are expressed as absolute value (%).
SAPS 2, Simplified Acute Physiology Score; COPD, Chronic Obstructive Pulmonary Disease; PEEP, Positive End-Expiratory Pressure; PaO_2/FiO_2, ratio of arterial oxygen tension to inspired oxygen fraction

Table 2. Threshold, area under the receiver operating characteristics curves (AUC-ROC), sensitivity, specificity, positive and negative likelihood ratios and positive and negative predictive values of endotracheal pressure induced by a bilateral phrenic nerve stimulation (Ptr,stim), diaphragm thickening fraction (TFdi) and rapid shallow breathing index (RSBI) to predict successful liberation from mechanical ventilation.

	Threshold	AUC-ROC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Likelihood ratios (95% CI)		Predictive Values (%) (95%	
					Positive	Negative	Positive	Negativ
Ptr,stim	7.8 cmH_2O	0.87 (0.75–0.94)	78 (60–91)	80 (59–93)	3.9 (1.7–8.7)	0.3 (0.1–0.5)	83 (69–92)	74 (59–8
TFdi	28.7 %	0.85 (0.73–0.93)	72 (53–86)	84 (64–95)	4.5 (1.8–11.3)	0.3 (0.2–0.6)	85 (70–94)	70 (57–8
RSBI	50 $breaths.min^{-1}.l^{-1}$	0.70 (0.56–0.81)	66 (47–81)	68 (47–85)	2.1 (1.1–3.8)	0.5 (0.3–0.9)	72 (58–83)	61 (47–7

CI: Confidence interval.

Legend of the figures

Figure 1. Flow chart of the study.

SBT: spontaneous breathing trial.

Figure 2. Receiver operating characteristics curves of endotracheal pressure induced by a bilateral phrenic nerve stimulation (**Ptr,stim**), diaphragm thickening fraction (**TFdi**), diaphragm excursion (**EXdi**), rapid shallow breathing index (**RSBI**), respiratory rate over TFdi (**RR/TFdi**) ratio and respiratory rate over EXdi (**RR/EXdi**) ratio to predict successful liberation from mechanical ventilation.

Figure 1

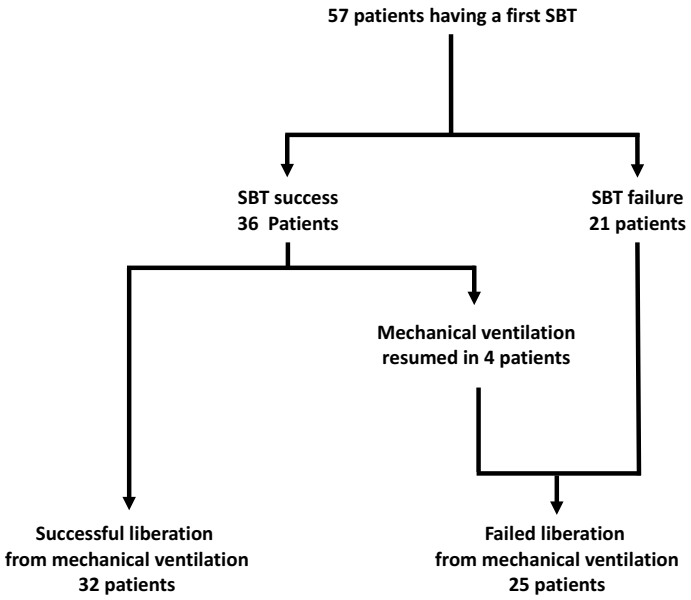
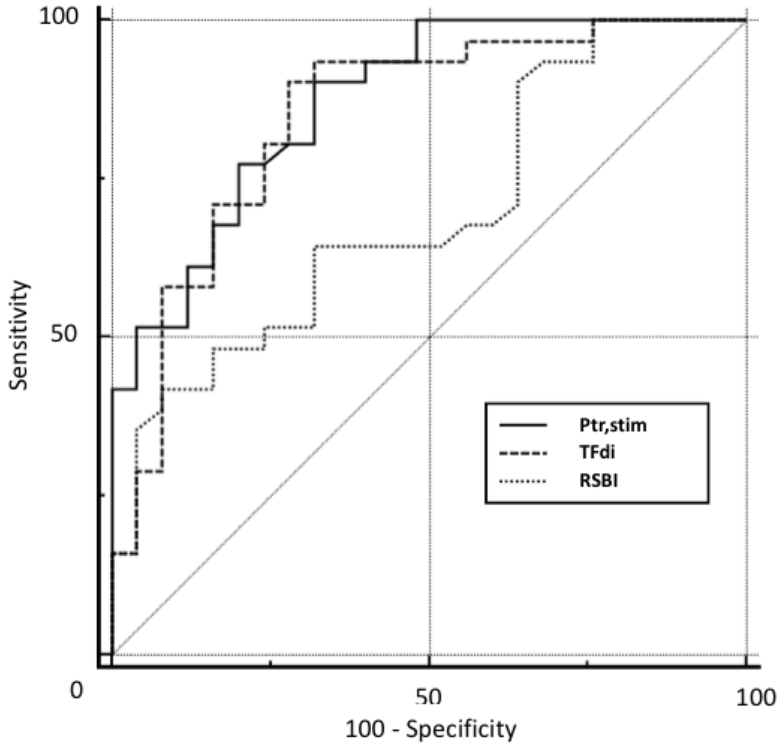

57 patients having a first SBT
SBT success
36 Patients
SBT failure
21 patients
Mechanical ventilation
resumed in 4 patients
Successful liberation
from mechanical ventilation
32 patients
Failed liberation
from mechanical ventilation
25 patients

Figure 2


100
50
0
Sensitivity
50
100
100 - Specificity
Ptr,stim
TFdi
RSBI

Diaphragm function and liberation from mechanical ventilation:

An ultrasound and phrenic nerve stimulation clinical study

Martin Dres, Ewan Goligher, Bruno-Pierre Dubé, Elise Morawiec, Laurence Dangers,

Danielle Reuter, Julien Mayaux, Thomas Similowski, Alexandre Demoule

Supplemental Digital Content

Text

Methods

Readiness criteria to initiate a spontaneous breathing trial (SBT)
Exclusion criteria
Criteria defining SBT failure
Description of the phrenic nerves stimulation technique
Description of the diaphragm ultrasound technique

Tables

Table SDC1. Results of the sensibility analysis looking at the performances of Ptr,stim, TFdi and RSBI to predict successful spontaneous breathing trial.

Table SDC2. Threshold, area under the receiver operating characteristics curves (AUC-ROC), sensitivity, specificity, positive and negative likelihood ratios and positive and negative predictive values of endotracheal pressure induced by a bilateral phrenic nerve stimulation (Ptr,stim), diaphragm thickening fraction (TFdi) and rapid shallow breathing index (RSBI) to predict successful liberation from mechanical ventilation in the validation cohort.

Methods

Readiness criteria to initiate a spontaneous breathing trial (SBT)

A SBT was initiated as soon as all the four following criteria were present [1]:

1) adequate oxygenation as stated by a SpO2 > 90 % on a fraction of inspired oxygen (FiO2) ≤ 40 % and positive end expiratory pressure (PEEP) ≤ 8 cmH_2O,
2) adequate pulmonary function as stated by a respiratory rate ≤ 35/min,
3) a cooperative cognitive state,
4) stable cardiovascular status as stated by a systolic arterial blood pressure of 90-160 mmHg without or minimal vasopressors and heart rate ≤140/min.

Exclusion criteria

Exclusion criteria were related to any contra-indications or impossibility to perform magnetic stimulation of the phrenic nerves among the following: cardiac pacemaker or implanted defibrillator, cervical implants, use of neuromuscular blocking agents within the 24 hours preceding the diaphragm function assessment (with the exception of succinylcholine used during rapid-sequence induction of anaesthesia for intubation), pre-existing neuromuscular disorders, factors possibly interfering with tracheal pressure measurements in response to phrenic stimulation (multiple functioning chest drains, intrinsic positive end expiratory pressure). Intrinsic positive end expiratory pressure was found when at relaxed end-expiration, the endotracheal pressure could not reach the zero baseline while the endotracheal tube was disconnected from the ventilator, manually occluded and by checking the absence of respiratory effort. Finally, age less than 18 years, known pregnancy, and a decision to withhold life-sustaining treatment were also exclusion criteria.

Criteria defining SBT failure

The presence of at least one of the five following criteria defined SBT failure [1]:

1) blood oxygen saturation (SpO_2) of < 90 % with a fraction of inspired oxygen (FiO_2) ≥ 50 %,
2) acute respiratory distress (RR ≥ 40/min, agitation, cyanosis),
3) systolic arterial blood pressure ≥ 180 mmHg or increase by ≥ 20 %,
4) heart rate ≥ 140/min or increase by ≥ 20 %,
5) respiratory acidosis defined as pH < 7.32 with an arterial carbon dioxide tension ($PaCO_2$) ≥ 50 mmHg.

If none of these failure criteria was present, the SBT was considered as successfully completed and the patient was extubated. The decision was ultimately taken by the attending physician.

Description of the phrenic nerves stimulation technique

Diaphragm pressure generating capacity was assessed in terms of the changes in endotracheal tube pressure induced by bilateral phrenic nerve stimulation during airway occlusion (Ptr,stim) as it has been already described elsewhere [2–4]. Phrenic nerve stimulation was performed by bilateral anterior magnetic stimulation. Briefly, two figure-of-eight coils connected to a pair of Magstim® 200 stimulators (The Magstim Company, Dyfed, UK) were positioned immediately posterior to the sternomastoid muscles at the level of the cricoid cartilage. Stimulations were delivered at the maximum output intensity of the stimulator (100%) that is known to consistently result in supramaximal phrenic contraction [3,5–7]. The patients were studied in a standardized semi-recumbent position, as follows: end-expiratory pressure was set to zero and the patient was allowed

to exhale during an end-expiratory pause. While the endotracheal tube was manually occluded, bilateral anterolateral magnetic stimulation was performed. The absence of active respiratory efforts in response to stimulation was determined by checking the stability of the airway pressure signal. Two operators were required to achieve both stimulation and measurements. After determining the optimal position of the coils, at least three stimulations were performed at 100% of maximal output allowed by the stimulator. Stimulations were separated by at least 60-sec to avoid superposition. The average of the three measures was taken into account for analysis. Ptr,stim was defined as the amplitude of the negative pressure wave following stimulation, taken from baseline to peak. It was measured at the proximal external end of the endotracheal tube, using a linear differential pressure transducer (MP45 ± 100 cmH_2O, Validyne, Northridge, Calif., USA). The pressure signal was sampled and digitized at 128 Hz (MP30, Biopac Systems, Santa Barbara, Calif., USA or Powerlab, AD Instruments, Bella Vista, Australia) for subsequent data analysis.

Description of the diaphragm ultrasound technique

Ultrasound measurements were performed by two investigators after a 2 months training session in diaphragmatic ultrasound. Inter-observer reliability of the ultrasound measurements has been described elsewhere [8].

Ultrasound assessment of the diaphragm thickening was performed using a 4-12 MHz linear array transducer (Sparq ultrasound system, Phillips, Philips Healthcare, Andover, MA, USA). As previously reported [9,10], the probe was placed perpendicular to the right chest wall, at the midaxillary line between the 9^{th} and 10^{th} right intercostal spaces (at the level of the zone of apposition) and the right diaphragm was identified as a

three-layered structure comprising two hyperechoic lines representing the pleural and peritoneal membranes and an middle hypoechoic layer representing the diaphragmatic muscle fibers. Using M-mode at a sweep speed of 10 mm/s, at least three spontaneous quiet breathing cycles were recorded and the image was frozen. Diaphragm thickness was measured at end-expiration (Tdi,ee) and end-inspiration (Tdi,ei) using electronic calipers. The thickening fraction of the diaphragm (TFdi) was calculated offline as (Tdi,ei – Tdi,ee)/ Tdi,ee.

Diaphragm excursion was measured using a 2-6 MHz broadband curved array transducer, with the same ultrasound machine. The probe was placed below the right costal margin and directed medially and cephalad. The diaphragm was identified as the hyperechoic linear structure cephalad to the liver, and its excursion measured using M-mode.

For all measurement, at least three valid breathing cycles were recorded, and the average of the individual values was reported. Ultrasounds were performed by one of the investigators (either B.P.D or M.D.).

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Tables

Table SDC1. Threshold, area under the receiver operating characteristics curves (AUC-ROC), sensitivity, specificity, positive and negative likelihood ratios and positive and negative predictive values of endotracheal pressure induced by a bilateral phrenic nerve stimulation (Ptr,stim), diaphragm thickening fraction (TFdi) and rapid shallow breathing index (RSBI) to predict successful spontaneous breathing trial.

	Threshold	AUC-ROC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Likelihood ratios (95% CI)		Predictive Values (%) (	
					Positive	Negative	Positive	Neg
Ptr,stim	7.2 cmH_2O	0.82 (0.70–0.91)	78 (61–90)	71 (48–89)	2.7 (1.4–5.5)	0.3 (0.2–0.6)	82 (70–90)	65 (4
TFdi	23.6 %	0.83 (0.70–0.91)	75 (58–89)	76 (53–92)	3.2 (1.4–6.9)	0.3 (0.2–0.6)	84 (72–92)	64 (4
RSBI	50 $breaths.min^{-1}.l^{-1}$	0.66 (0.53–0.78)	61 (44–77)	67 (43–85)	1.8 (0.0–3.5)	0.6 (0.4–1.0)	76 (62–86)	50 (3

Table SDC2. Threshold, area under the receiver operating characteristics curves (AUC-ROC), sensitivity, specificity, positive and negative likelihood ratios and positive and negative predictive values of endotracheal pressure induced by a bilateral phrenic nerve stimulation (Ptr,stim), diaphragm thickening fraction (TFdi) and rapid shallow breathing index (RSBI) to predict successful liberation from mechanical ventilation in the validation cohort.

	Threshold tested	AUC-ROC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Likelihood ratios (95% CI)		Predictive Values (%) (	
					Positive	Negative	Positive	Neg
Ptr,stim	7.8 cmH_2O	0.82 (0.57–0.95)	78 (40–97)	70 (35–93)	2.6 (0.9–7.1)	0.3 (0.1–1.2)	70 (46–87)	78 (4
TFdi	28.7 %	0.81 (0.57–0.95)	78 (40–97)	90 (56–99)	7.8 (1.2–51.6)	0.3 (0.1–0.9)	88 (51–98)	88 (5
RSBI	50 $breaths.min^{-1}.l^{-1}$	0.70 (0.45–0.88)	44 (14–79)	90 (56–99)	4.4 (0.6–32.8)	0.6 (0.3–1.1)	80 (35–97)	64 (4

CI: confidence interval.

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REVIEW

Critical illness-associated diaphragm weakness

Martin Dres[1,2,3*], Ewan C. Goligher[4,5], Leo M. A. Heunks[6] and Laurent J. Brochard[3,5]

Abstract

Diaphragm weakness is highly prevalent in critically ill patients. It may exist prior to ICU admission and may precipitate the need for mechanical ventilation but it also frequently develops during the ICU stay. Several risk factors for diaphragm weakness have been identified; among them sepsis and mechanical ventilation play central roles. We employ the term critical illness-associated diaphragm weakness to refer to the collective effects of all mechanisms of diaphragm injury and weakness occurring in critically ill patients. Critical illness-associated diaphragm weakness is consistently associated with poor outcomes including increased ICU mortality, difficult weaning, and prolonged duration of mechanical ventilation. Bedside techniques for assessing the respiratory muscles promise to improve detection of diaphragm weakness and enable preventive or curative strategies. Inspiratory muscle training and pharmacological interventions may improve respiratory muscle function but data on clinical outcomes remain limited.

Keywords: Diaphragm dysfunction, Respiratory muscle weakness, Critically ill patients, Diaphragm atrophy

Introduction

Skeletal muscle is a highly organized tissue, providing structural support, locomotion, breathing, shape, facial expression, and metabolic support to the body. The muscles of the respiratory system are precisely organized to facilitate inspiratory and expiratory air flow for respiration, airway clearance, and speech. The action of the diaphragm (the main inspiratory muscle) is usually quantified in terms of force generation (measured by inspiratory pressures) or shortening (measured by lung volume change or displacement of chest wall structures). Diaphragm weakness is defined as the inability of the diaphragm to generate normal levels of maximal force.

Accumulating evidence suggests that diaphragm weakness develops in a majority of critically ill patients exposed to mechanical ventilation [1–5]. The diaphragm is the main respiratory muscle and has a vital role in ventilation, but the prevalence and impact of diaphragm weakness have been often neglected with few recommendations for prevention and treatment. Different risk factors for critical illness-associated diaphragm weakness have been identified. Diaphragm weakness may preexist and precipitate respiratory failure. Acute diaphragm injury and weakness may also result from sepsis, trauma, systemic inflammation, or mechanical ventilation [6]. The wide range of potential injury mechanisms probably explains the high prevalence of diaphragm weakness observed in the ICU both in the early [2] and later stages of critical illness [3, 5]. We employ the term critical illness-associated diaphragm weakness to refer to the phenomenon of diaphragm weakness occurring in critically ill patients regardless of the cause and the timing. Herein we discuss the definition, prevalence, pathophysiology, and clinical consequences of critical illness-associated diaphragm weakness. We also discuss potential preventive and therapeutic strategies and highlight future avenues for research.

The normal diaphragm

The diaphragm is a thin, dome-shaped muscular structure separating the thoracic and abdominal cavities.

*Correspondence: martin.dres@aphp.fr
[2] Service de Pneumologie et Réanimation Médicale, Groupe Hospitalier Pitié-Salpêtrière-Charles Foix, La Pitié Salpêtrière Hospital, 47-83 BLD de l'Hôpital, 75013 Paris Cedex 13, France
Full author information is available at the end of the article

Under normal conditions, the diaphragm acts much like a piston within a barrel, generating flow as its dome descends and displaces the abdominal contents beneath [7]. The pressure generated across the dome between the thoracic and abdominal cavities is called the transdiaphragmatic pressure (Pdi) and is proportional to the tension developed within the muscle fibers. The magnitude of the pressure swings on either side of the diaphragm depends on the volume change induced by diaphragmatic contraction and the elastance of the thorax and abdomen. For simplicity, the maximal Pdi is used as a global measure of diaphragm muscle force.

Techniques for monitoring diaphragm activity in critically ill patients

Diaphragm activity refers to the contractile forces generated by the muscle to maintain adequate ventilation under conditions of varying load. Strength refers to the maximal force-generating capacity of the muscle. These quantities can be assessed by the amount of pressure generated by diaphragm contraction. Hence, diaphragm force is evaluated on the basis of the pressure generated during maximal volitional inspiratory efforts (Pdi,max) or by non-volitional calibrated stimulation of the phrenic nerve (Table 1) [8].

The gold standard for assessing diaphragm force is measurement of Pdi generated by twitch magnetic stimulation of the phrenic nerves (Pdi,tw) [9]. The principal advantage of Pdi,tw is that it provides a standardized measure of pressure generation that is independent of the patient's effort. This technique is performed by applying magnetic coils powered at their maximal output over the cervical portion of the phrenic nerves bilaterally (Fig. 1). Although not entirely identical to Pdi,tw, the twitch pressure generated at the outside tip of the endotracheal tube (Pet,tw) can be regarded as a surrogate of Pdi,tw that does not require esophageal and gastric balloons [9]. Pet,tw is now used widely in studies investigating diaphragm force [2–5].

Diaphragm electromyography (EMG) can be used to assess diaphragm activity. The introduction of neurally adjusted ventilatory assist (NAVA), a ventilator mode that synchronizes ventilation to diaphragm electrical activity using a dedicated nasogastric tube with EMG electrodes, has greatly facilitated the bedside monitoring of crural diaphragm activity (EAdi). The ratio of

Table 1 Techniques for assessing diaphragm force and activity in critically ill patients

	Markers of		Cutoff defining diaphragm weakness
	Diaphragm activity	Diaphragm force	
Ultrasound			
TFdi			
Requires a high frequency linear probe	Tidal TFdi	TFdimax	<20% [15]
EXdi			
Requires a low frequency abdominal probe Patient disconnected from ventilator	EXdi	Max EXdi	<1 cm [17]
Pressure			
Pdi			
Requires esophageal and gastric balloons	Pdi	Pdimax	Pdimax <60 cmH_2O [8]
Pdi,tw Pet,tw			
Require magnetic stimulation	–	Pdi,tw	<−10 cmH_2O [8]
		Pet,tw	<−11 cmH_2O [9]
ΔPga/ΔPdi			
Incorrect placement of the gastric balloon in the lower esophagus and recruitment of abdominal muscles mimic severe diaphragmatic weakness	–	ΔPga/ΔPdi	<0 [8]
Electromyography			
EMG			
Requires surface electrodes and offline analysis	RMS	–	Not defined
EAdi			
Requires dedicated ventilator	EAdipeak	EAdimax	Not defined

TFdi diaphragm thickening fraction, *EXdi* diaphragm excursion, *Pdi* transdiaphragmatic pressure, *Pdi,max* maximal transdiaphragmatic pressure, *Pet,tw* endotracheal pressure induced by bilateral magnetic stimulation of the phrenic nerves, *Pdi,tw* transdiaphragmatic pressure induced by bilateral magnetic stimulation of the phrenic nerves, *ΔPga/ΔPdi* ratio of the inspiratory Pga swings to Pdi, *EMG* electromyogram, *EAdi* electrical activity of the diaphragm, *RMS* root mean square, *EAdipeak* peak of the EAdi signal, *EAdimax* EAdi during a maximal inspiratory effort

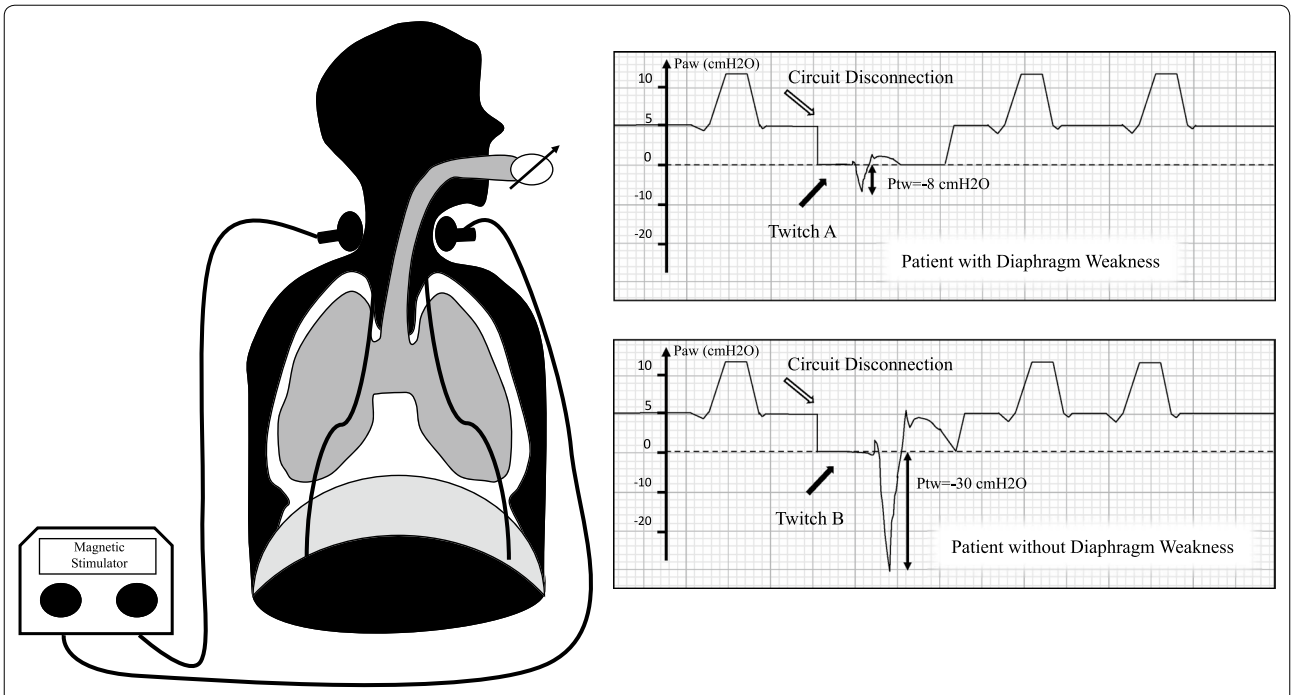

Fig. 1 Schematic representation of the phrenic nerve stimulation technique in patients ventilated with pressure support mode. Two magnetic coils are positioned at the initial portion of the phrenic nerves. Airway pressure is recorded at the tip of the endotracheal tube. First, the circuit is disconnected (white arrow) and twitches are generated by a magnetic stimulator (full black arrows). Diaphragm weakness is assessed by the amount of airway pressure generated during a magnetic twitch. Twitch A is followed by a reduced capacity to generate pressure (−8 cmH_2O) [9], whereas twitch B is followed by normal drop of pressure (−30 cmH_2O)

actual EAdi to maximum EAdi (EAdi,max) can be used to estimate the patient's effort to breathe [10]. For a given patient, EAdi is tightly correlated to the pressure generated by the diaphragm under various levels of ventilatory assistance [10]. EAdi is a promising tool to monitor diaphragm activity [11]; however, EAdi,max varies widely between subjects so that there is no clear reference range for EAdi.

Diaphragm ultrasound provides a direct visualization of the diaphragm. As the diaphragm contracts, it thickens, and the magnitude of the increase in thickness during inspiration can be expressed as a percentage increase in thickness (the thickening fraction of the diaphragm, TFdi) (Fig. 2). TFdi reflects the activity of the muscle during tidal breathing and provides an estimate of its strength during a maximal inspiratory effort (TFdi,max) [12]. There is a wide range of TFdi values: it is 0–5% in patients under neuromuscular blockade [13]; it ranges between 20% and 50% in spontaneously breathing patients after extubation [14]. TFdi is correlated with both the pressure–time product of the diaphragm and with EAdi [13, 14]. Some studies suggest that TFdi obtained during a maximal inspiratory effort [15] or quiet breathing in mechanically ventilated patients [16] can be employed to assess diaphragm force. Finally, ultrasound can also measure maximal diaphragm excursion, a marker that predicts extubation success and failure with reasonable sensitivity and specificity [17]. This latter index can only be interpreted during non-assisted breathing; otherwise the downward displacement of the diaphragm may reflect passive insufflation of the chest by the ventilator.

Definition and prevalence of critical illness-associated diaphragm weakness

The pressure-based definition of diaphragm weakness using Pdi,tw is considered as the reference method but the Pet,tw method is easier to measure in the ICU [9]. Using the latter, one can define diaphragm weakness as a Pet,tw below 11 cmH_2O [8, 18]. Several studies have characterized the prevalence of diaphragm weakness using this criterion (Table 2). With this definition, within 24 h after intubation, diaphragm weakness is present in up to 64% (54/85) of patients [2]. At the time of weaning, diaphragm weakness is present in between 63% [5] and 80% of patients [1, 3]. Approximately 80% of patients requiring prolonged mechanical ventilation exhibit diaphragm weakness [9, 19].

Ultrasound can also be used to define diaphragm weakness. Diaphragm excursion less than 1.1 cm during tidal

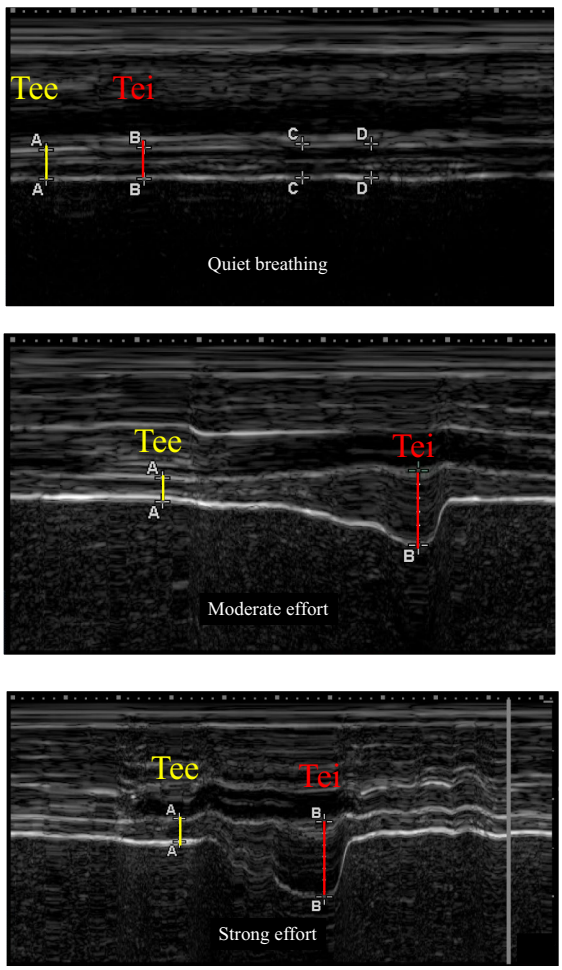

Fig. 2 Diaphragm ultrasound using time-motion mode at three different conditions: quiet breathing, moderate inspiratory effort, and strong inspiratory effort. Note the increase in diaphragm end inspiratory thickness (Tei) at moderate and strong inspiratory effort. *Tee* end expiratory thickness, *Tei* end inspiratory thickness

breathing also defines diaphragm weakness [17]. Maximal TFdi below 20% is diagnostic of severe diaphragm weakness [15]. Studies employing the ultrasound-based definition of diaphragm weakness report that 29% of patients (24/82) have diaphragm weakness at the first spontaneous breathing trial [17] and 36% (20/55) at extubation [20].

Overlap with limb muscle acquired weakness

Critical illness polyneuropathy [21, 22] and myopathy are the major causes of limb weakness and wasting in the ICU. An extensive revision of the literature on ICU acquired weakness with indication on future research was recently published in this journal [23]. Mechanical ventilation may impose bed rest and may indirectly prolong immobility as a result of the use of sedatives or neuromuscular blocking agents which in turn may promote neuropathy, muscle wasting, and loss of muscle function [24]. Although it was initially thought to be rare, neuromuscular dysfunction is found in up to 25% of ICU patients requiring mechanical ventilation for more than 7 days [25]. While the diaphragm is characterized by a permanent cyclic activity, other striated muscles such as limb muscles are not constantly active. Furthermore, although both diaphragm and limb muscle are striated muscles, their fiber type composition differs [26]. Thus, the consequences of prolonged unloading of the diaphragm may be distinct from the consequences of unloading limb muscles, as demonstrated by experimental and clinical studies [27, 28]. At the time of weaning, diaphragm weakness is twice as frequent as limb muscle weakness [5] and patients with diaphragm weakness are no more or less likely to have limb muscle weakness [5]. While they share common features, diaphragm and limb muscle weakness likely represent two distinct entities with different pathophysiology.

Causes and mechanisms of critical illness-associated diaphragm weakness

Respiratory muscle weakness in critically ill patients may result from hyperinflation, neuropathies, myopathies, metabolic abnormalities, decreased oxygen delivery, and medications [29]. Myopathies are subdivided into several categories that include critical illness myopathy, sepsis-associated myopathy, ventilator-associated respiratory muscle injury, disuse atrophy, metabolic disturbances, and medications [29]. Another classification based on histology may be useful [21] but consideration of muscle unexcitability without muscle structural disarrangement is also possible [30]. In the sickest patients, it is likely that multiple factors take effect simultaneously. In addition, some factors (sepsis, injuriously high inspiratory efforts) present before admission in the ICU can contribute to diaphragm weakness and may in fact precipitate the need for mechanical ventilation. Certain patient factors may also prevent diaphragm weakness: one experimental model suggested a protective role for obesity [31]. We now summarize the complex interplay of contributors to diaphragm weakness before admission and during the ICU stay (Fig. 3).

Mechanisms of diaphragm weakness at the time of ICU admission

Hypercapnic respiratory failure

Acute hypercapnia increases neural drive through chemoreflex activation; its effects on diaphragm contractility during spontaneous breathing are conflicting. In one study conducted in healthy subjects exposed to acute

Table 2 Prevalence of diaphragm weakness with different definitions and settings

Studies	Settings	Prevalence
Ultrasound studies		
Kim et al. [17]	Weaning	24/82 (29%)
Jiang et al. [20]	Weaning	20/55 (36%)
DiNino et al. [99]	Weaning	15/66 (23%)
Pressure studies		
Demoule et al. [2]	On admission	54/85 (64%)
Watson et al. [9]	Stable ICU patients	26/33 (79%)
Supinski and Callahan [19]	Stable ICU patients	48/57 (84%)
Jung et al. [3]	Weaning	32/40 (80%)
Laghi et al. [1]	Weaning	12/16 (75%)
Dres et al. [5]	Weaning	48/76 (63%)
Lerolle et al. [50]	Post cardiac surgery	19/28 (68%)

ICU Intensive care unit

changes in CO_2, diaphragm force was reduced [32]. Separately, hypercapnia did not intensify long-lasting fatigue but slightly reduced diaphragm contractility immediately after maximum voluntary ventilation [33]. However, no significant change in twitch pressure was reported while subjects breathed CO_2 [34] or produced maximal contraction [33]. In vitro, respiratory acidosis induces diaphragm weakness in non-ventilated rats whereas metabolic acidosis has no effect [35]. In clinical practice, acute hypercapnia could contribute to clinical deterioration by favoring diaphragm weakness.

Cardiogenic shock

Cardiogenic shock is associated with both an increase in diaphragm work and a reduction in diaphragm oxygen delivery. The imbalance between oxygen supply and demand can ultimately result in diaphragm fatigue. This was demonstrated in dogs exposed to cardiogenic shock with tamponade, in which a marked reduction in Pdi was noted after 1 h despite an increase in central drive, ultimately causing death [36] (Fig. 4). Low cardiac output impairs respiratory muscle blood flow and the diaphragm may shift to anaerobic metabolism resulting in muscular lactate production [37]. Mechanical ventilation and muscle paralysis spare a large fraction of cardiac output used by the working respiratory muscles [38]. In one study highlighting the critical importance of respiratory muscle failure in shock states, spontaneously breathing dogs

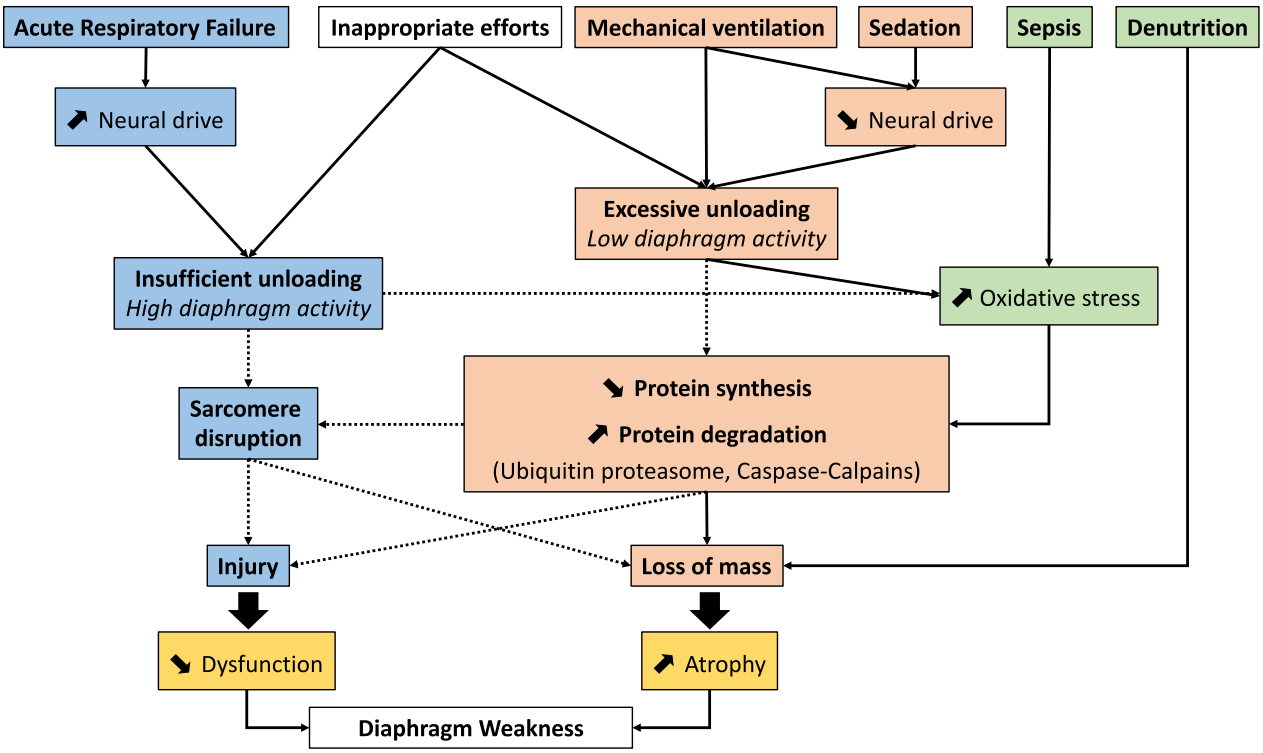

Fig. 3 Schematic illustration of mechanisms pathways involved in the occurrence of diaphragm weakness in critically ill patients. Note that the figure ignores cases of unexcitable muscle in which muscle injury may be reduced or nonexistent. Dashed lines represent uncertain causation and full black lines represent established causation

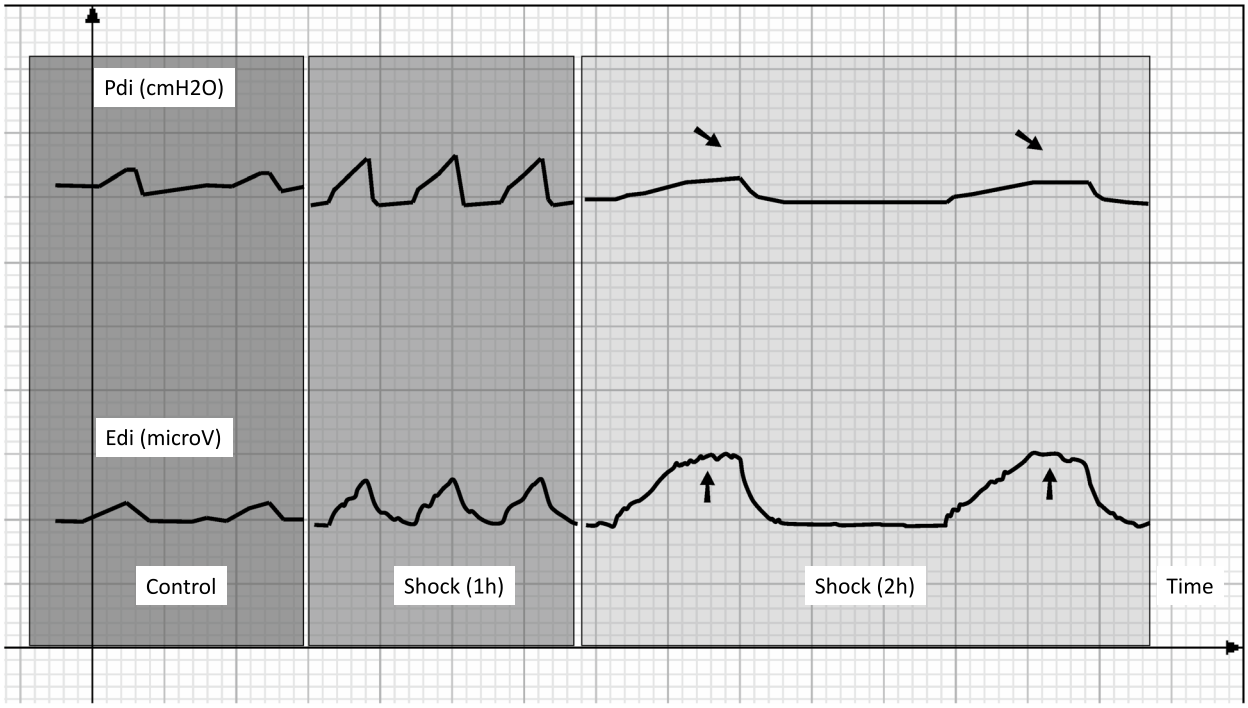

Fig. 4 Schematic illustration of the effect of cardiogenic shock on transdiaphragmatic pressure (Pdi) and diaphragm electrical activity (Edi). While cardiogenic shock induced an important increase in Edi, late course is marked by a decrease in Pdi as a surrogate of diaphragm fatigue. Adapted from Aubier et al. [36]

with cardiogenic shock were much more likely to die from ventilatory failure compared to mechanically ventilated dogs [37].

Sepsis

Both severe diaphragm weakness and increased susceptibility to injury and fatigue have been documented in animal models of sepsis [39–41]. Sepsis impairs diaphragm force apart from any effect on muscle mass or architecture [41], suggesting an important role for systemic inflammation. Sepsis acts at two levels [42]. First, disturbances in different steps of the chain of muscular energy supply including altered blood flow distribution (hypoxic ischemia) and use (cytopathic ischemia). Second, direct impairment of the contractile proteins resulting from the action of septic mediators such as cytokines can also result in dysfunction. Tumor necrosis factor alpha (TNF-α) has been shown to mediate the detrimental effects of endotoxin administration on the contractile function of the diaphragm [43].

Systemic inflammation also renders the diaphragm more sensitive to load-related injury, possibly by increasing sarcolemma membrane fragility [44]. In septic rats undergoing controlled mechanical ventilation, sepsis exacerbated diaphragm weakness resulting from controlled mechanical ventilation [45]. In the ICU, patients with sepsis are more likely to exhibit diaphragm atrophy [46]. Sepsis can be present early during the ICU stay as a primary reason for admission or later, complicating the course. Interestingly, experimental findings suggest that mechanical ventilation could alleviate the harmful effects of sepsis on diaphragm function [44]. Sepsis is associated with diaphragm weakness in more than half of mechanically ventilated patients [2, 19], and the potential interactions between sepsis and mechanical ventilation on diaphragm function require greater attention.

Surgery

Abdominal surgery, in particular of the upper abdomen, is associated with postoperative respiratory complications in which diaphragm dysfunction is frequently implicated [47, 48]. Although pain or general anesthesia may contribute to the phenomenon, pain relief does not ameliorate postoperative diaphragm force [49] and general anesthesia performed for lower abdominal surgery does not lead to diaphragm weakness. The attenuated phrenic nerve output following stimulation of visceral or somatic phrenic afferent pathways during surgery has been proposed as a possible alternate mechanism [29]. Diaphragm

weakness has also been reported after coronary bypass surgery [48, 50]. In this case, the phrenic nerve can be directly injured (surgical manipulations, ischemia, cardioprotection) leading to left hemidiaphragm or bilateral weakness with important clinical consequences.

Risk factors for diaphragm weakness during ICU course

Sedatives, steroids, and neuromuscular blocking agents

Sedatives may have direct adverse effects on the diaphragm as well as promoting disuse. In patients undergoing anesthesia for elective surgery, propofol induces a decrease in the diaphragm's capacity to generate pressure [51]. In ICU patients, the dose of propofol was correlated with the severity of diaphragm weakness [52]. Volatile anesthetics, some not in use anymore [53], have also been shown to cause diaphragm weakness [54].

Corticosteroids have been associated with the development of critical illness myopathy [25, 55]. Corticosteroids may affect contractile function of striated muscles by inhibition of protein synthesis and activation of protein degradation pathways. Nevertheless, the effects of corticosteroids on the diaphragm are not entirely predictable and may vary according to the regimen of administration, the specific corticosteroid, muscle fiber type, and possibly species. Importantly, corticosteroid doses administered in animal studies are often much higher than doses employed in clinical practice [56]. The effects of corticosteroids on diaphragm in ICU patients are therefore complex, but it is likely that diaphragm weakness is more severe with higher doses and a longer duration of exposure. Accordingly, administration of corticosteroids should be carefully guided by judicious evaluation of expected benefits and harm. While neuromuscular blockers are used to adapt patients to the ventilator, they render the diaphragm inactive and may contribute to diaphragm disuse and consequent atrophy. A particular concern exists when neuromuscular blockers are administrated in conjunction with glucocorticoids [55]. In animal models, rocuronium (aminosteroidal non-depolarizing neuromuscular blocker) exacerbates diaphragm weakness induced by controlled mechanical ventilation [57]. By contrast, cisatracurium (a non-steroidal benzyl isoquinoline non-depolarizing neuromuscular blocker) does not exacerbate the effects of ventilation on diaphragm force [58]. Importantly, when used for a short period (48 h) at the early phase of ARDS, cisatracurium did not induce ICU-acquired limb muscle weakness and increased ventilator-free days [59].

Mechanical ventilation

Mechanical ventilation has been clearly identified as a contributor to diaphragm weakness. It can be associated with adverse effects on respiratory muscles through two potentially competing mechanisms (Fig. 3): (1) disuse atrophy secondary to diaphragm inactivity from excessive ventilatory support, (2) load-induced injury due to insufficient ventilatory support and (3) hypercapnia under controlled mechanical ventilation.

Disuse atrophy

Just a few hours of fully controlled mechanical ventilation leads to rapid-onset atrophy and decreased contractile force both in vitro and in vivo [60–63]. Conversely, partially assisted mechanical ventilation mitigates atrophy and diaphragm weakness [61, 64]. Findings from animal models are difficult to replicate in critically ill patients who are frequently exposed to many risk factors for diaphragm injury. The first evidence in humans came from a study in 1988 by Knisely et al. who reported diaphragm atrophy in a postmortem series of neonates requiring long-term ventilation [65]. Twenty years later, Levine et al. found histological evidence of diaphragm atrophy among 14 adult brain-dead organ donors after meeting brain death criteria for 18–69 h [28]. Importantly, pectoralis muscle was unaffected in these patients over the same period of inactivity, suggesting that the rapid atrophy is specific to the diaphragm [28]. Diaphragm muscle fiber dysfunction is not only due to loss of muscle mass in these patients: the reduction in myofibrillar contractility also arises from deranged cross-bridge formation [66]. Diaphragm biopsies obtained from a heterogeneous group of ICU patients demonstrated the development of muscle fibers atrophy, activation of proteolysis, enhanced number of inflammatory cells in the muscle, and development of muscle fiber weakness [66]. Interestingly, force-generating capacity of the muscle fibers was reduced even after correction for loss of contractile protein, demonstrating the development of contractile protein dysfunction [66]. Although studies in animals and brain-dead patients suggested an important role for mitochondrial dysfunction and oxidative stress in the development of diaphragm dysfunction during mechanical ventilation [28, 67], mitochondrial morphology and function appeared normal in the diaphragm of ICU patients [68]. In addition, markers for oxidative stress and antioxidant enzymes in the diaphragm were not different between ICU and control patients [68].

Two studies reported a progressive decline of diaphragm force in vivo with increasing duration of mechanical ventilation [4, 52]. In a series of 76 patients, Dres et al. found that although the duration of mechanical ventilation from intubation to weaning was associated with the occurrence of diaphragm dysfunction, this effect did not persist in a multivariable analysis incorporating other risk factors [5]. More than mechanical ventilation itself, it is the unloading of the diaphragm under

mechanical ventilation which is the critical contributor of diaphragm weakness. While the precise mechanism underlying disuse atrophy is debated [69], the deleterious effects of diaphragm unloading are strongly supported by experimental [60, 61] and clinical [70] data demonstrating that diaphragm atrophy and weakness can be attenuated by maintaining some level of respiratory muscle loading during ventilation.

Assuming that atrophy may be detected with ultrasound, Grosu et al. described a time-dependent decrease in diaphragm thickness in seven patients [71]. It was confirmed in larger cohorts [70, 72]. Goligher et al. reported a rapid decrease in diaphragm thickness in over 40% of mechanically ventilated patients [70]. Importantly, diaphragm atrophy occurred quickly and the largest magnitude in the change of diaphragm thickness was achieved by day 4. Moreover, the change in diaphragm thickness over time was related to the level of inspiratory effort [70]. Importantly, diaphragm thickness was relatively stable on days when diaphragm thickening fraction (a measure of inspiratory effort) was consistent with normal resting breathing [70].

Excessive loading

Excessive respiratory muscle loading can result in diaphragm injury, as demonstrated in both animal and human studies [73]. Tracheal banding (prolonged resistive loading) in hamsters resulted in ventilatory failure associated with diaphragm injury characterized by susceptibility of myofibrillar complexes to calpain-mediated degradation [74]. Diaphragm injury in this context is characterized by myofibrillar disarray and inflammatory infiltration [73]. Sepsis appears to sensitize the sarcolemma to stress-related injury (membrane hyperfragility) [44]. Load-induced diaphragm injury has also been demonstrated in humans, manifesting as a prolonged loss of force production after resistive loading [75] and sarcomere disruption on histology [76].

Eccentric contractions—where the muscle contracts as it is lengthened—may be particularly injurious [77]. Eccentric contractions may occur in the context of patient–ventilator dyssynchrony [77]. Contractile activity of the diaphragm during expiratory diaphragm lengthening was recently demonstrated in acute hypoxemic respiratory failure [78]. Whether eccentric contractions are sufficiently frequent and severe to cause diaphragm weakness in mechanically ventilated patients is unknown.

The concept of load-induced injury may explain recent findings showing increases in diaphragm thickness—possibly reflecting muscle inflammation and edema—in a subset of mechanically ventilated patients associated with high levels of inspiratory effort [70]. Insufficient or delayed unloading of the respiratory muscles in the context of acute respiratory failure may therefore contribute to diaphragm injury.

Hypercapnia under controlled ventilation

The effect of hypercapnia on diaphragm force under mechanical ventilation has been studied in experimental models. In ventilated and anesthetized piglets, acute and short exposure (6 h) to hypercapnia induces a marked reduction in diaphragm force as assessed by phrenic nerve stimulation [79]. However, when piglets are exposed to prolonged duration of mechanical ventilation (72 h), hypercapnia limited the occurrence of ventilator-induced diaphragm dysfunction (VIDD) [80], a finding that was confirmed in vitro [81]. Whether hypercapnia occurring in a patient failing a weaning test contributes to diaphragm weakness is unknown.

Clinical consequences of diaphragm weakness

Irrespective of whether it is present at admission [2] or at a later stage [3, 5, 19], diaphragm weakness is a marker of illness severity and of poor prognosis. Diaphragm weakness diagnosed at the time of ICU admission demonstrates that critical illness can impair diaphragm function even before the patient is admitted to the ICU. At the early stage of critical illness, diaphragm weakness is analogous to any other form of organ dysfunction and its presence is associated with higher mortality [2]. To what extent diaphragm weakness can contribute to a poor prognosis has not been elucidated. Importantly, diaphragm weakness can improve despite exposure to mechanical ventilation [82]. Similar to a reversible septic cardiomyopathy, sepsis-related diaphragm weakness observed upon admission may be readily reversible. Nevertheless, the time of course and the determinants of the recovery need to be clarified in further studies. The extent to which early diaphragm weakness [2] constitutes a risk factor for later critical illness-associated diaphragm weakness is unknown. Diaphragm weakness detected after several days of mechanical ventilation is strongly associated with weaning failure [3, 5, 17, 50]. Diaphragm weakness entails limited physiological reserve in the face of new pulmonary insults. In isolation, it is usually not sufficient to precipitate respiratory failure, but in the presence of high ventilatory demands or deteriorating respiratory mechanics it may rapidly result in weaning or extubation failure. Diaphragm weakness can indeed also be present in patients who are successfully liberated from ventilation [3, 5]. Some findings already suggest a high risk of hospital readmission in patients with chronic respiratory failure in case of respiratory muscle weakness 7 days after ICU discharge [83]. Another study reported increased mortality after 1 year [84]. Further research looking at the impact of diaphragm weakness on

long-term survival, exercise tolerance, and quality of life is therefore warranted.

Prevention and treatment of diaphragm weakness

Prevention strategies

Table 3 summarizes a number of strategies aimed at preventing and treating diaphragm weakness in critically ill patients. Animal studies [64] and recent clinical investigations [70] suggest that maintaining spontaneous breathing under mechanical ventilation should minimize diaphragm atrophy. Muscle-protective ventilation strategies should therefore aim at titrating ventilation (and sedation) to maintain appropriate levels of inspiratory muscle effort and minimize patient–ventilator asynchrony [85].

In specific circumstances such as ARDS, some preliminary findings suggest that spontaneous breathing could be directly harmful to the lungs by generating or worsening lung injury [86], in particular in patients with high respiratory drive. Preliminary exploratory data suggest that in these patients control of the level of respiratory muscle activity and tidal volume with partial neuromuscular blockade could be feasible [87]. Monitoring diaphragm activity is possible at the bedside through NAVA catheter, esophageal catheter, or diaphragm ultrasound. Further studies are needed to determine the upper and lower boundaries of the amount of diaphragm activity preventing diaphragm atrophy and subsequent dysfunction and diaphragm injury. Monitoring P0.1 as an index of respiratory drive is also a potentially useful technique to guide the ventilator titration [88]. Proportional assist ventilation and NAVA are two modes during which the level of respiratory muscle activity can be monitored [10, 89]. Diaphragm pacing has been investigated in experimental [90] and human [91] studies suggesting that intermittent contractions of the diaphragm may prevent atrophy. This strategy has been applied through a transvenous phrenic nerve pacing system designed to be percutaneously placed in the left subclavian vein. Additionally, pharmacologic approaches aiming at targeting mitochondrial and cellular pathways of diaphragm dysfunction are currently being investigated [92].

Management strategies

Hypophosphatemia impairs the contractile properties of the diaphragm during acute respiratory failure [93]. In the case of weaning failure, the level of plasmatic phosphatemia may be therefore monitored and corrected if required [94]. There has been great interest in improving diaphragm inotropy, by using inhibition of phosphodiesterase (PDE)3 and PDE4 (theophylline, 1,3-dimethylxanthine) [95] or calcium sensitizer levosimendan [96]. Theophylline has been extensively studied but has a narrow non-toxic therapeutic range. A retrospective cohort analysis reported improvement in diaphragm movements in 21/40 patients with VIDD who received low-dose theophylline [97]. Levosimendan has been shown to reverse diaphragm contractility in healthy subjects exposed to loaded breathing [96]. A randomized clinical trial (NCT01721434) is currently investigating whether

Table 3 Strategies to prevent and to treat diaphragm weakness in mechanically ventilated patients

Preventive strategies	Level of evidence	Clinical recommendations
Prevention of disuse atrophy		
Maintaining inspiratory efforts	High (experimental and clinical data)	Spontaneous breathing should be preferred (except in case of high drive)
Phrenic nerve pacing	Low (experimental data)	Not in routine practice
Inspiratory muscles training		
Progressive threshold loading	Moderate (clinical data)	Can be implemented in specific populations (long-term ventilation)
Pharmacological approach		
Antioxidants (*N*-acetylcysteine)	Low (experimental and clinical data)	Not recommended
Curatives or rescue techniques		
Phrenic nerve pacing		
Restoring progressively diaphragm function	Low (only experimental data)	Not in routine practice
Pharmacological approach		
Anabolics	Low (experimental data)	Not in routine practice
Optimization of muscle contractility		
Theophylline	Moderate (experimental and clinical data)	Not in routine practice
Levosimendan	Moderate (experimental and clinical data)	Not in routine practice

levosimendan could facilitate liberation from the ventilator. Inspiratory muscle training can be instituted to enhance muscle endurance or strength. It is a strategy that can be achieved with rehabilitation protocols that use progressive threshold loading [98]. Although an attractive approach, inspiratory muscle training has not been well tested and proven as an intervention enabling one to improve clinical outcomes significantly. As a treatment, diaphragm pacing may be interesting in difficult-to-wean patients as it is currently under investigation (NCT03096639).

Conclusion

There is an expanding body of evidence showing both that diaphragm force is influenced by many factors in the ICU and that diaphragm weakness is frequent. The right balance between lung protective mechanical ventilation strategy and maintaining diaphragm activity has to be better investigated and may be challenging for clinicians. Monitoring diaphragm activity may prove to be necessary. Diaphragm ultrasound is a promising tool for monitoring diaphragm activity but the optimal range of inspiratory effort warrants further investigation. In addition, the potential recovery of diaphragm weakness after extubation should be determined. It may provide guidance for future therapies.

Author details
[1] Neurophysiologie Respiratoire Expérimentale et Clinique, Sorbonne Universités, UPMC Université Paris 06, INSERM, UMRS_1158, Paris, France. [2] Service de Pneumologie et Réanimation Médicale, Groupe Hospitalier Pitié-Salpêtrière-Charles Foix, La Pitié Salpêtrière Hospital, 47-83 BLD de l'Hôpital, 75013 Paris Cedex 13, France. [3] Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada. [4] Department of Medicine, Division of Respirology, University Health Network and Sinai Health System, Toronto, Canada. [5] Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada. [6] Department of Intensive Care Medicine, VU University Medical Centre Amsterdam, Amsterdam, The Netherlands.

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Compliance with ethical standards

Conflicts of interest
MD gave lectures for Pulsion Medical Systems. LB's research laboratory received research grants and/or equipment from Covidien, General Electric, Fisher Paykel, Maquet (with St. Michael's Hospital), and Philips. LH received speakers fee from Maquet Critical Care and Orion Pharma. His lab received research grants from Orion Pharma and Liberate Medical. EG declares no conflict of interest.

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RESUME

La dysfonction diaphragmatique, au même titre que la neuromyopathie de réanimation qui touche les membres périphériques sont des causes fréquemment impliquées dans l'échec du sevrage de la ventilation mécanique. Des données suggèrent que ces deux atteintes sont le reflet d'une même affection ayant un tropisme respiratoire et locomoteur. Cette thèse met en évidence que la dysfonction diaphragmatique et la neuromyopathie de réanimation sont deux atteintes distinctes dont la coexistence est relativement faible. De plus, la dysfonction diaphragmatique a un impact délétère plus important sur le sevrage et le pronostic vital que la neuromyopathie de réanimation. Toutefois, le niveau de fonction diaphragmatique requis pour permettre une séparation du ventilateur est plus faible que le niveau de fonction définissant la dysfonction diaphragmatique. Ce travail montre également que l'exploration de la fonction diaphragmatique peut être simplifiée par l'utilisation de l'échographie et de l'électromyographie du diaphragme.

Mots clés : diaphragme, ventilation mécanique, sevrage, extubation, neuromyopathie de réanimation

Abstract

Diaphragm dysfunction and critical illness associated neuropathy and myopathy are frequently suspected to cause weaning failure from mechanical ventilation. Some data suggest that both may be gathered into a same entity with two localisations, respiratory and peripheral. This thesis highlights that diaphragm dysfunction and critical illness neuromyopathy are two distinct diseases that don't frequently coexist. In addition, diaphragm dysfunction has a more severe impact on weaning outcome and prognosis than critical illness associated neuromyopathy and myopathy. However, the level of diaphragm function required to ensure safe mechanical ventilation discontinuation is lower than the level of diaphragm function defining diaphragm dysfunction. This work also shows that investigating diaphragm function may be simplified by the use of ultrasound and diaphragm electromyogram activity.

Key words: diaphragm, mechanical ventilation, weaning, extubation, critical illness associated neuropathy and myopathy