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UNIVERSITE PARIS EST CRETEIL
Ecole doctorale Sciences de la Vie et de la Santé

THESE

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Champ disciplinaire : Pathologie et Recherche Clinique

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Emmanuel VIVIER

**EXPLORATION DE LA FONCTION MUSCULAIRE RESPIRATOIRE ET DE
L'AMYOTROPHIE DES PATIENTS DE SOINS INTENSIFS.
INTERET DES TECHNIQUES ECHOGRAPHIQUES**

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Rapporteur : Pr Jean Christophe RICHARD

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Résumé

Contexte Le diaphragme des patients de soins critiques subit une agression fréquente et précoce principalement en rapport avec la ventilation mécanique et le sepsis. Cette agression entraîne une dysfonction diaphragmatique souvent méconnue dans les premiers jours de réanimation car cliniquement silencieuse. Au moment de la levée de sédation, elle peut se révéler un facteur pronostic décisif sur la durée de sevrage ventilatoire, la durée de séjour et la survie. Des méthodes simples et robustes sont nécessaires pour mieux caractériser certaines propriétés du diaphragme des patients de réanimation : sa trophicité, sa puissance et son couplage à la ventilation mécanique. L'échographie est une technique simple et accessible qui permet l'observation superficielle et en profondeur de ce muscle respiratoire. **Objectifs** Comprendre et préciser la signification physiologique de différents indices échographiques utilisables par le clinicien pour aborder le diaphragme. Caractériser l'atrophie musculaire associée aux premiers jours de ventilation mécanique. Déterminer la pertinence de l'échographie du diaphragme dans différentes situations cliniques : aide à la décision d'extubation et dépistage des asynchronies patient-ventilateur. **Populations et Méthodes** Trois études cliniques prospectives descriptives (dont une multicentrique) et une étude chez le volontaire sain ont servi de support à la thèse. **Résultats** La fraction d'épaississement mesurée au niveau de la zone d'apposition du diaphragme semble corrélée au travail respiratoire chez des patients sous ventilation non invasive mais l'indice est influencé par de multiples facteurs et sa précision affaiblie par une variabilité élevée. Une atrophie du diaphragme pendant les cinq premiers jours de ventilation est visualisable par échographie de la zone d'apposition et ne semble pas corrélée à l'atrophie du pectoral. Ni l'excursion, ni l'épaississement mesurés après réussite d'une épreuve de ventilation spontanée et avant extubation ne peuvent aider à prédire l'issue de l'extubation. En revanche l'observation combinée des mouvements diaphragmatiques enregistrés en mode temps-mouvement couplés aux courbes de pression des voies aériennes permet le dépistage et la caractérisation des principales asynchronies en ventilation non invasive chez le volontaire sain. **Conclusion** L'échographie permet d'investiguer l'atrophie du diaphragme en réanimation.

L'appréciation du travail respiratoire par la fraction d'épaississement doit tenir compte des nombreuses limites de cet indice. L'échographie du diaphragme semble peu judicieuse pour orienter la décision d'extubation en réanimation mais pourrait être pertinente pour dépister et caractériser les principales asynchronies patient-ventilateur sous ventilation non-invasive.

Mots clés

Diaphragme ; Amyotrophie ; Sevrage ventilatoire ; Asynchronies ; Echographie

Summary

Background Patient diaphragms experience frequent and early aggression related to mechanical ventilation and sepsis in critical care. This aggression causes a diaphragmatic dysfunction which is often underestimated in the first days of ICU stay because it is clinically silent. It can however be a decisive prognostic factor associated with duration of weaning from mechanical ventilation, length of stay and mortality. Simple and robust methods are needed to better characterize some diaphragm properties in ICU: its trophicity, strength and coupling to mechanical ventilation. Ultrasound is a simple and accessible technique that allows superficial and deep observation of the diaphragm.

Objectives Understand and clarify the physiological significance of the different ultrasound indices that can be used by the clinician to explore the diaphragm. Characterize the muscular atrophy associated with the first days of mechanical ventilation. Determine the relevance of diaphragm ultrasound in different clinical situations: support for the order-to-extubate decision and screening for patient-ventilator asynchronies.

Populations and Methods Three descriptive prospective clinical studies (including one multicenter) and one study in healthy volunteers were used to support the thesis. **Results** Measurement of the thickening fraction of the diaphragm in zone of apposition appears to be correlated with work of breathing in patients under non-invasive ventilation, but the index is influenced by multiple factors and its precision weakened by a high variability. An atrophy of the diaphragm during the first five days of ventilation is noticeable by ultrasound in zone of apposition and does not seem to correlate with the atrophy of the pectoralis. Neither the excursion nor the thickening fraction measured after a successful spontaneous breathing test and before the extubation can help to predict its success. On the other hand, the combined analyze of diaphragmatic movements in time-motion mode and airway pressure curves makes it possible to diagnosis and characterize the main asynchronies in noninvasive ventilation in healthy volunteer.

Conclusion Ultrasound enables the investigation of the diaphragm atrophy in ICU. The appreciation of the respiratory work of breathing by the thickening fraction of thickening must be tempered by the numerous limits of this index. The diaphragm ultrasound seems injudicious to guide the decision

to extubate in ICU but could be relevant to detect and characterize the main patient-ventilator asynchronies under non-invasive ventilation.

Key Words

Diaphragm; Amyotrophy; Weaning from mechanical ventilation; Asynchrony; Ultrasound

Résumé pédagogique

Les patients de soins intensifs doivent souvent être sédatisés et placés sous ventilation artificielle à la phase initiale de leur hospitalisation. Cette mise au repos du système respiratoire entraîne une altération de la force du diaphragme, préjudiciable pour la suite du séjour. L'échographie est une technique simple et accessible qui permet l'observation du diaphragme par différentes méthodes. L'objet de cette thèse est d'en préciser la signification et l'intérêt clinique. Il ressort de ces travaux que (1) l'épaississement du diaphragme est mesurable là où il s'appose à la paroi thoracique et que cet épaississement est corrélé au travail respiratoire. (2) Cet indice est faiblement reproductible et soumis à de multiples influences. (3) Une amyotrophie du diaphragme peut être observée au même site pendant les cinq premiers jours de ventilation mécanique. (4) L'échographie du diaphragme ne permet pas d'orienter le clinicien dans sa décision d'extubation. (5) Couplée au monitoring des pressions du circuit respiratoire, l'échographie du diaphragme permet le dépistage des asynchronies entre patient et respirateur lors de la ventilation non invasive.

Educational summary

Patients are usually sedated and placed under invasive mechanical ventilation during the initial course of ICU stay. Stopping the voluntary ventilation causes an alteration of the diaphragm strength, which could be detrimental for the patient prognosis. Ultrasound is a simple and accessible technique that allows observation of the diaphragm by different methods. The purpose of this thesis is to clarify the meaning and the clinical implications of the exam. From this work, it can be concluded that: (1) The thickening of the diaphragm can be assessed in the zone of apposition and this thickening rises with increased work of breathing. (2) This index is poorly reproducible and is influenced by numerous parameters. (3) Amyotrophy of the diaphragm may be observed at the same site during the first five days of mechanical ventilation. (4) Diaphragm ultrasound couldn't guide the clinician's decision for extubation. (5) Combined analysis of airway pressure curves and diaphragm ultrasound allows the detection of patient-ventilator asynchronies during non-invasive ventilation.

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Préambule et introduction

L'assistance respiratoire des patients critiques permet de maintenir les échanges gazeux, éviter l'épuisement cardio-respiratoire et prévenir les complications neurologiques lors d'une agression systémique. Ainsi, la ventilation mécanique à pression positive est une technique consubstantielle à la réanimation. Elle a participé à sa genèse lors des grandes épidémies européennes de poliomyélite (Copenhague 1952), et l'avancée des connaissances à son sujet ponctue l'histoire de la spécialité : curarisation, recrutement alvéolaire, ventilation non invasive, décubitus ventral, ventilation protectrice... Mais cette histoire a également été marquée par la prise de conscience progressive d'effets secondaires en lien avec la ventilation artificielle : infections nosocomiales, contrainte cardiocirculatoire, barotraumatisme alvéolaire, troubles du sommeil, delirium...

Parmi ces effets collatéraux, émerge depuis une vingtaine d'année le concept de dysfonction diaphragmatique. Induite dès les premiers jours de ventilation, elle a longtemps été méconnue du clinicien en raison de son caractère silencieux. Cette affection fonctionnelle et structurelle pourrait toutefois se révéler un déterminant majeur du sevrage ventilatoire, le processus décisif qui conduit le patient depuis la guérison de sa pathologie initiale vers l'extubation.

Mais le diaphragme est un organe peu visible, difficile d'abord et complexe, à la fois dans sa structure et dans sa fonction. Ce muscle aussi vital que le cœur assure une fonction simple, la pérennité de la ventilation 24h/24. La compréhension et l'évaluation des mécanismes qui permettent l'adaptation de cette fonction à l'environnement nécessitent des méthodes d'investigation cliniques dynamiques, robustes et reproductibles.

A ce titre, l'échographie est particulièrement intéressante. De par sa maniabilité et sa précision, elle s'est imposée au lit des malades critiques au cours de ces vingt dernières années, en particulier pour observer le cœur des malades. Et c'est assez naturellement que les réanimateurs ont réorienté leurs sondes vers le diaphragme des patients ventilés : ils ont ainsi pu observer son

excursion et son épaissement. Il est alors devenu tentant de demander à l'échographie de répondre à certaines questions :

- Le diaphragme est-il fonctionnel ou paralysé, trophique ou atrophié ?
- Le patient est-il bien adapté au respirateur, et si non pourquoi ?
- Le soutien apporté par le respirateur est-il excessif ou insuffisant ?

Encore fallait-il comprendre les images enregistrées et interpréter les indices mesurés, afin de positionner précisément l'échographie au sein de l'ensemble des examens disponibles pour explorer le diaphragme en réanimation. C'est l'objet de cette thèse.

La première partie esquisse une synthèse des connaissances concernant le diaphragme et la dysfonction diaphragmatique, les moyens d'investigations disponibles en réanimation, ainsi que la place émergente de l'échographie dans ce contexte. La seconde partie est organisée autour de trois travaux cliniques et une étude réalisée chez le volontaire sain, rapportés ici sous la forme de trois articles publiés et un manuscrit soumis. Ces quatre travaux abordent successivement les questions suivantes :

- (1) Quels sont les déterminants de l'épaississement diaphragmatique ? Existe-t-il une association entre épaissement diaphragmatique et neuromyopathie de réanimation ?
- (2) Une amyotrophie du diaphragme est-elle observable par échographie pendant les cinq premiers jours de ventilation ? Si oui, cette amyotrophie atteint-elle plus spécifiquement les patients ventilés de manière invasive ? Concerne-t-elle plus spécifiquement le diaphragme que les autres muscles non impliqués dans la ventilation (ex : pectoral) ?
- (3) La réalisation d'une échographie du diaphragme peut-elle aider le clinicien dans sa décision d'extubation, lorsqu'un patient fragile a réussi une épreuve de sevrage ?
- (4) L'échographie du diaphragme en mode temps-mouvement couplée au défilement des courbes de pression permet-elle de repérer et caractériser les principales asynchronies en ventilation non-invasive ?

I. Synthèse des connaissances

Cette synthèse a pour objectif (1) de faire un état des lieux des connaissances concernant l'anatomie et la physiologie du diaphragme, (2) décrire les connaissances acquises ces 30 dernières années concernant la dysfonction diaphragmatique de réanimation, (3) lister les principales techniques accessibles en réanimation pour évaluer les performances des muscles respiratoires et (4) présenter les différentes techniques échographiques permettant l'exploration du diaphragme en réanimation.

1 Le diaphragme, un protagoniste majeur de la ventilation

1.1 Anatomie du diaphragme

Le diaphragme est une structure musculo-tendineuse qui sépare et cloisonne la cavité thoracique de l'abdomen. Il se présente sous la forme d'une double coupole dessinant un dôme transversal. La coupole droite est un peu plus apicale que la gauche et les insertions musculaires sont plus caudales en arrière. La partie centrale du dôme est une structure horizontale tendineuse perforée de trois hiatus, ouvrant le passage aux gros vaisseaux (veine cave inférieure, aorte et canal thoracique) et à l'œsophage (*Cf. Figure 1*). Elle est partiellement au contact direct de la partie inférieure du péricarde. Le corps musculaire a une situation périphérique et est composé de fibres musculaires striées de type I et II. Ces fibres sont digastriques, c'est-à-dire qu'elles présentent deux corps musculaires positionnés en série et séparés par un tendon musculaire intermédiaire (l'ensemble de ces tendons formant le centre tendineux). Ainsi les fibres musculaires diaphragmatiques striées sont-elles les seules du corps humain à ne pas exercer une action pour rapprocher deux os.

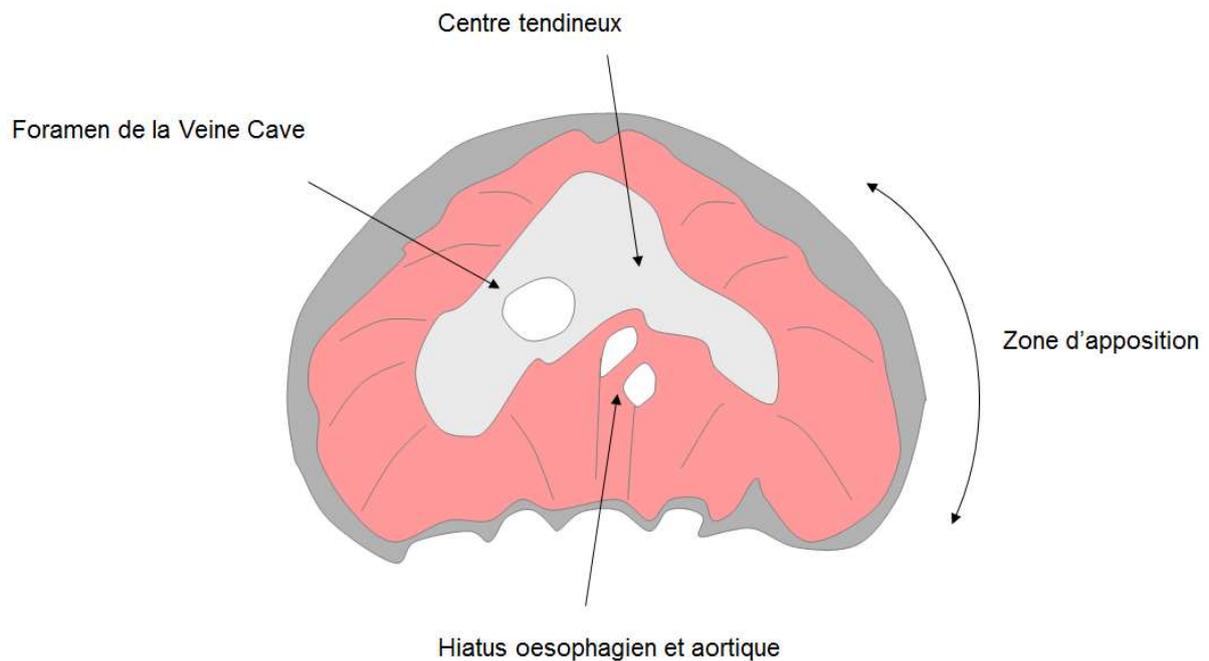
Depuis le centre tendineux rayonnent donc des fibres musculaires qui s'insèrent en périphérie sur des structures osseuses : en avant sur la face postérieure de l'appendice xiphoïde du sternum (portion sternale), latéralement sur les cartilages des six dernières côtes (portion costale) et en

arrière sur la face antéro-latérale des quatre premières vertèbres lombaires par l'intermédiaire des piliers du diaphragme (portion vertébrale). L'arcade du psoas (ou ligament centré médial) s'appuie sur les vertèbres de T12 à L3 tandis que l'arcade du carré des lombes (ligament arqué latéral) relie l'apophyse transverse au sommet de la 12^{ème} côte. Les fibres sont assez clairsemées en cette zone, créant le hiatus costo-lombaire, brèche reliant anatomiquement les espaces pleuraux et péritonéaux.

Les fibres antéro-latérales (insertions costales et xiphoïdiennes) définissent le diaphragme costal, tandis que les fibres postérieures (insertions vertébro-lombaires) constituent le diaphragme crural. Il est démontré chez l'animal que le segment costal et le segment crural ont des origines embryologiques et une innervation différente (1,2) et peut-être une fonction légèrement différente (3). L'insertion des fibres à destination costale est plus ou moins régulière, pouvant aller jusqu'à former de véritables invaginations diaphragmatiques au sein du parenchyme hépatique (appelées « slips »). Ces anomalies d'insertions sont plus fréquentes avec l'âge et pourraient concerner jusqu'à 30% des patients (4,5).

La disposition périphérique des fibres musculaires diaphragmatiques explique leur orientation verticale chez le sujet sain. Elles tendent toutefois à s'horizontaliser avec l'augmentation du volume thoracique. En arrière des côtes, les fibres musculaires du diaphragme viennent même totalement s'accoler à la paroi thoracique sur plusieurs centimètres avant de s'engrener par digitation avec celles du muscle transverse de l'abdomen. Cette zone où le diaphragme est apposé à la paroi thoracique est nommée « zone d'apposition » et présente un intérêt échographique car elle est peu profonde et souvent échogène en raison des séreuses qui l'encadrent (plèvre et péritoine). Wait a montré chez le chien que la zone d'apposition costale est proportionnellement plus épaisse que la zone crurale (6). Cette zone sera d'autant plus réduite que le sujet présente une distension thoracique (7).

Figure 1. Anatomie du diaphragme



1.2 Vascularisation du diaphragme

Le diaphragme présente une vascularisation très riche marquée par de nombreuses afférences et une grande densité capillaire. Sa finalité physiologique est de maintenir un flux artériel suffisant quelles que soient les circonstances, en particulier en situation de baisse du débit cardiaque (8,9). Les artères diaphragmatiques dessinent ainsi une double arborisation sur la face thoracique et sur la face abdominale du muscle. Sur la face supérieure, les artères musculophréniques et péricardiophréniques (diaphragmatiques supérieures) proviennent des artères thoraciques internes (mammaires internes) tandis que les artères phréniques supérieures proviennent directement de l'aorte thoracique. Sur la face inférieure, les artères phréniques inférieures (diaphragmatiques inférieures) sont les premières collatérales de l'aorte abdominale ; elles peuvent parfois provenir du tronc cœliaque. Une troisième voie de vascularisation est rendue possible par le biais des artères intercostales. Les trois vascularisations (phréniques, mammaires et intercostales) s'anastomosent pour former une suppléance en cas d'abolition de l'un des flux (10). L'importante

microvascularisation permet d'adapter les apports cellulaires rapidement à la demande métabolique en fonction de l'activité du muscle grâce à un phénomène de recrutement capillaire (11).

1.3 Innervation du diaphragme

L'innervation du diaphragme est assurée par les deux nerfs phréniques droit et gauche se distribuant chacun vers une hémicoupe. Les nerfs phréniques proviennent du plexus cervical et sont issus des branches antérieures des nerfs spinaux des segments C3 à C5 de la moelle épinière, et principalement de C4. Ils relaient l'intégralité du signal moteur à l'origine de la contraction du muscle. Les fibres sensibles, en revanche (douleur et proprioception) sont doublées par des fibres à destination des nerfs intercostaux et subcostaux (en ce qui concerne la périphérie du muscle). Le nerf phrénique contient également des afférences sensibles provenant de la plèvre, du péricarde et du péritoine sus-mésocolique. Le nerf phrénique traverse le cou en avant du scalène antérieur, puis passe entre l'artère et la veine subclavière avant de plonger dans le thorax, longeant le médiastin de part et d'autre. Le nerf phrénique droit se divise en deux faisceaux antérieurs et postérieurs. Le nerf phrénique gauche se divise en de multiples faisceaux. L'ensemble de ces faisceaux permettent l'innervation des fibres musculaires sur les deux faces du muscle. Le trajet anatomique du nerf phrénique explique qu'une section accidentelle ou collatérale puisse survenir lors de toute chirurgie médiastinale ou thoracique profonde (12–15). Par ailleurs, il peut être lésé sur son trajet cervical lors de la pose d'un cathéter (16–18) ; cette disposition anatomique explique également la possibilité d'une paralysie phrénique après anesthésie locorégionale par bloc interscalénique (19,20). C'est également par voie cervicale qu'il sera possible de stimuler artificiellement le nerf phrénique afin de produire une contraction de l'hémicoupe homolatérale (21).

1.4 La fibre musculaire diaphragmatique

Le diaphragme est un muscle strié squelettique. La taille des fibres musculaires diaphragmatiques est relativement faible par rapport à celle des muscles périphérique (22). Il est composé de 50-55% de fibres musculaires lentes de type I, de 20-25% de fibres musculaires rapides de type IIa et 25% de fibres musculaire rapides IIb (23). Les fibres de type I sont riches en mitochondries et pauvres en enzymes glycolytiques. Elles ont un métabolisme principalement aérobie leur conférant une vitesse de contraction lente mais une forte résistance à la fatigue. A l'inverse les fibres IIb sont riches en enzymes glycolytiques et pauvres en mitochondries. Elles ont un mécanisme anaérobie permettant une contraction rapide mais générant une faible résistance. Les fibres IIa ont des propriétés intermédiaires. Chez le patient BPCO, on a décrit une augmentation des fibres de type I aux dépens de fibres de type II, comme mécanisme d'adaptation à l'effort (24).

Par ailleurs, les fibres musculaires diaphragmatiques sont plus riches en myoglobine que les muscles striés périphériques et caractérisées par un important système anti-oxydant (superoxyde dismutase, glutathion peroxydase) (25). Ce haut potentiel oxydatif est complété par une faible distance de diffusion entre capillaire et cellule musculaire (22). Ces propriétés confèrent à la fibre musculaire une grande résistance à la fatigue et constitue une protection contre les agressions oxydantes. La masse diaphragmatique est proportionnelle à la masse maigre de l'organisme chez le sujet sain (26).

1.5 Rôle du diaphragme en physiologie respiratoire

1.5.1 La commande ventilatoire

Le stimulus à l'origine de la contraction des fibres musculaires respiratoires provient des centres respiratoires situés au niveau du tronc cérébral. La respiration spontanée est cependant dirigée et régulée par une double commande. La commande automatique rythmique de siège ponto-

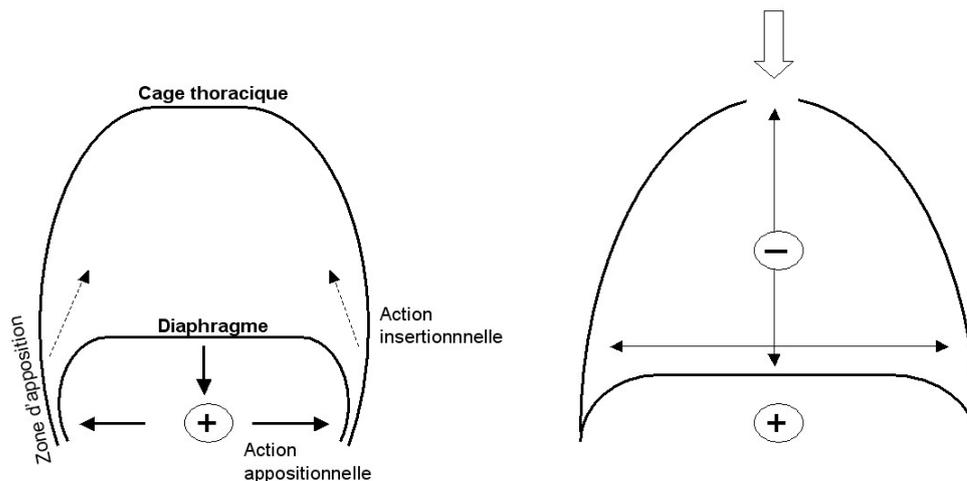
bulbaire est en effet régulée par des afférences volontaires ou involontaires d'origine corticale et bulbaire. Les deux commandes interagissent l'une avec l'autre pour garantir le maintien d'une ventilation vitale de base (rythmogénèse), tout en permettant son adaptation aux conditions homéostatiques (effort, sommeil, perturbation métabolique) et sa coordination avec les fonctions supérieures volontaires (apnée, manœuvres respiratoires) ou involontaires (parole, toux, défécation, accouchement). Ces neurones « respiratoires » envoient en particulier un signal électrique intégré vers les motoneurones spinaux cervicaux (C3-C5) dont les ramifications axonales innervent les plaques motrices diaphragmatiques via les deux nerfs phréniques. De leur côté, les muscles intercostaux sont innervés par les racines T1 à T12 et les scalènes par les racines C4 à C8.

1.5.2 Mécanique respiratoire

L'action du diaphragme est étroitement coordonnée avec celle des autres muscles inspiratoires. En effet, les intercostaux externes et les scalènes stabilisent le thorax pendant l'inspiration tandis que les muscles dilatateurs des voies aériennes permettent de réduire au maximum les résistances des voies aériennes.

La contraction des fibres musculaires diaphragmatiques entraîne un double mouvement, conjuguant raccourcissement de la portion musculaire et descente du dôme vers le contenu abdominal par un effet « piston ». Cette descente provoque une augmentation de hauteur de la cavité thoracique tout en générant une pression positive dans la cavité abdominale et une compression des viscères abdominaux (*Cf. Figure 2*).

Figure 2 : Mécanique diaphragmatique



La contraction et le durcissement du diaphragme développent deux forces complémentaires et simultanées, en rapport avec la conformation géométrique très particulière du squelette thoracique :

- Une force appliquée à la face interne des côtes basi-thoraciques et dirigée de dedans en dehors. Cette action est dite « appositionnelle ».
- Un mouvement de traction vers le haut et de rotation externe des dernières côtes (action « insertionnelle »).

L'association de ces deux forces complémentaires, conjuguée à la géométrie de l'articulation costo-vertébrale et l'orientation en bas et en avant du berceau costal conduit à l'augmentation paradoxale du diamètre transversal de la base du thorax et à une augmentation de la surface de section du gril costal (alors que les fibres musculaires se raccourcissent).

Lors de l'inspiration normale, l'augmentation des volumes du thorax et celle de l'abdomen sont synchrones. L'augmentation des dimensions de la cage thoracique confrontée à sa structure rigide, crée une pression intra-thoracique négative. Cette dépression transmise via la plèvre au système bronchiolo-alvéolaire et aux voies aériennes est à l'origine d'un flux d'air inspiratoire entrant. La contraction diaphragmatique entraîne donc simultanément une pression positive dans l'abdomen et une pression négative dans le thorax. La différence de pression entre ces deux compartiments,

appelée « pression transdiaphragmatique » est positive et croît à l'inspiration. La valeur de cette pression reflète la « force efficace » résultante de cette contraction. La relaxation diaphragmatique accompagne l'expiration, qui passive, dépend des forces de rappel de la paroi thoracique.

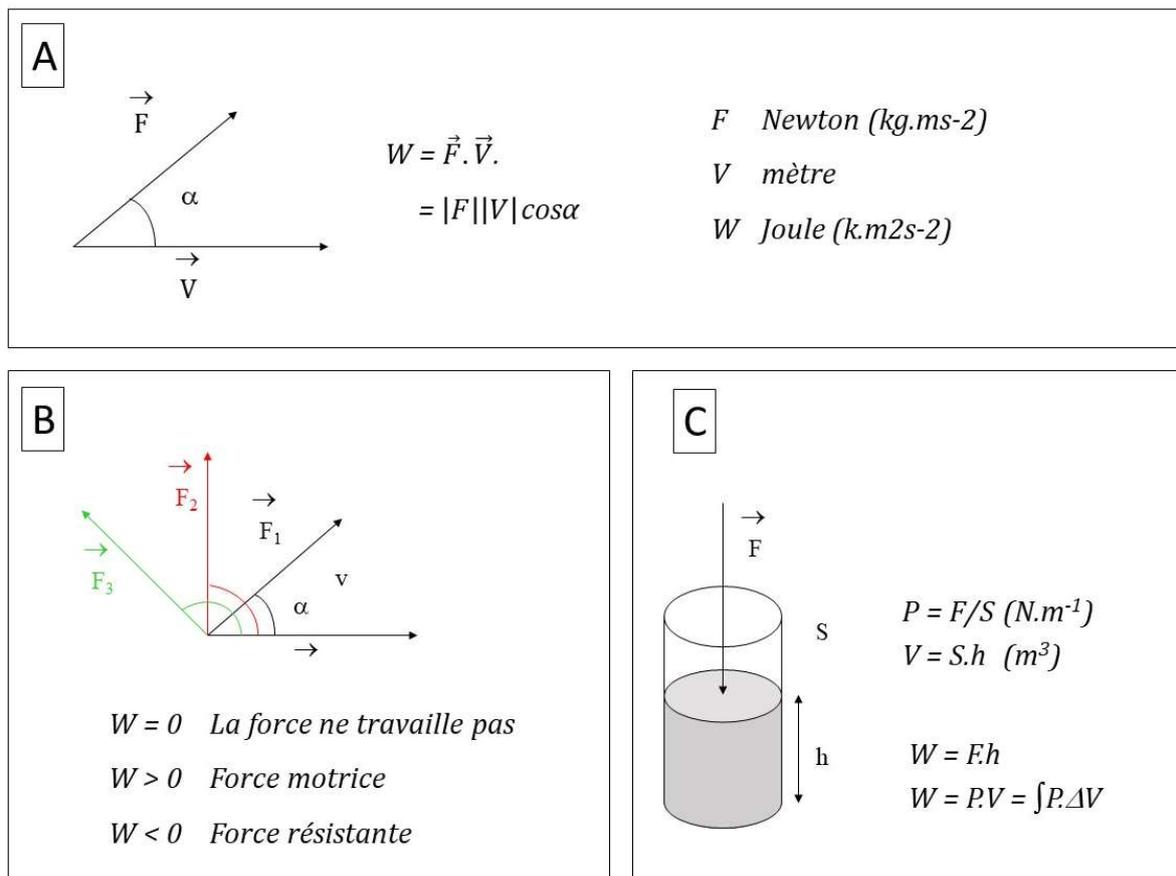
1.5.3 Notion de travail respiratoire

1.5.3.1 Notion physique et physiologique de travail

Le travail mécanique d'une force (W) est l'énergie produite par cette force lorsque son point d'application se déplace. Il peut se calculer comme le produit vectoriel de la force par son déplacement (Cf. *Figure 3A*). L'unité de mesure est le joule, une unité d'énergie. En fonction du travail développé par une force sur un système, on parle de force motrice ($W>0$), force résistante ($W<0$) ou force à travail nul ($W=0$) (Cf. *Figure 3B*).

En physiologie, cette notion peut être appliquée à un muscle ou à un groupe musculaire. Le travail musculaire est défini par le produit de la force musculaire exercée par le déplacement généré. Si on applique cette définition à un modèle de piston de seringue, le travail nécessaire pour mobiliser le volume de gaz contenu dans la seringue en appliquant une pression donnée peut également s'exprimer sous la forme du produit Pression x Volume (Cf. *Figure 3C*).

Figure 3. Illustration de la définition du travail d'une force sous forme d'un produit vectoriel (A et B) ou du produit pression volume (C).



W, travail ; *F*, Force ; *V*, Déplacement ; *S*, Surface ; *h*, hauteur, *V*, Volume ; *P*, Pression.

1.5.3.2 Le travail respiratoire

Les forces développées par les muscles respiratoires (principalement à l'inspiration) doivent vaincre les résistances élastiques de la cage thoracique et du parenchyme pulmonaire, mais aussi les résistances des voies aériennes. Lorsqu'on s'intéresse au système respiratoire, le travail représente l'énergie produite pour mobiliser le volume d'air nécessaire aux échanges gazeux. En assimilant le thorax à une seringue dont le diaphragme serait le piston, le déplacement considéré est alors la variation de volume pulmonaire, la force exercée est la pression motrice qui permet le mouvement et le travail s'écrit comme le produit :

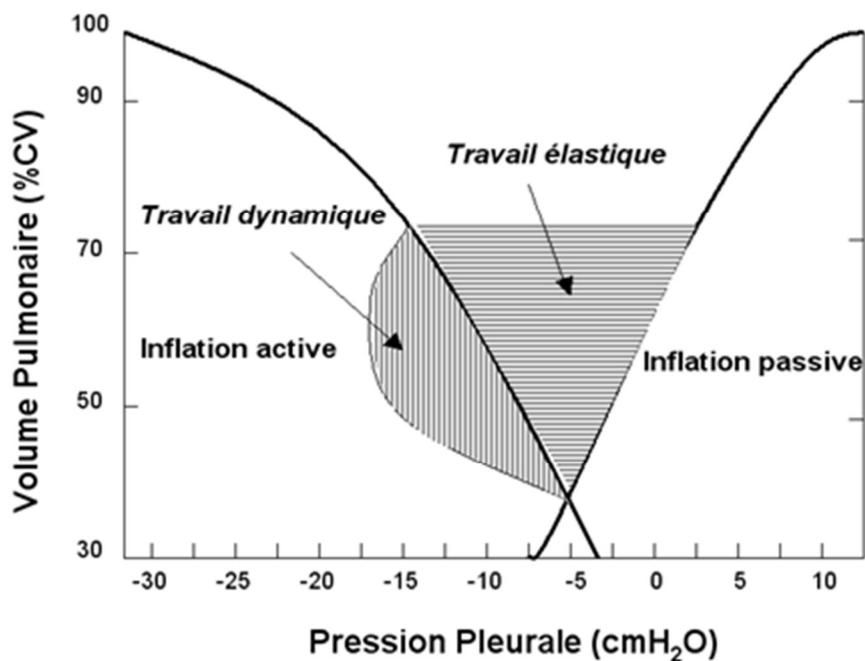
$$W = P.V = \int P.\Delta V$$

Le travail respiratoire est alors mesuré par unité de temps (puissance, dont l'unité est le Watt) ou par litres de ventilation (joules/l).

1.5.3.3 Mesure du travail respiratoire chez un patient ventilé

La méthode de référence pour le calcul du travail respiratoire repose sur l'analyse de la boucle pression-volume en utilisant le diagramme de Campbell (*Cf. Figure 4*). Le travail représente alors la surface définie par la courbe pression-volume. Mais cette technique n'est pas applicable en routine en réanimation pour les deux raisons suivantes : elle ne s'applique pas aux efforts isométriques (efforts à voies aériennes fermées, efforts inefficaces à déclencher le respirateur) et une partie de la modification du volume est assurée par l'énergie du respirateur et ne correspond pas directement au travail musculaire.

Figure 4 : Diagramme de Campbell. Analyse graphique du travail des muscles inspiratoires pendant un cycle respiratoire. En ordonnée : le volume pulmonaire exprimé en % de la capacité vitale (%CV). En abscisse : pression pleurale (cmH₂O). Hachures verticales : travail nécessaire pour vaincre la résistance des voies aériennes. Hachures horizontales : travail nécessaire pour surmonter les propriétés élastiques du poumon et de la cage thoracique



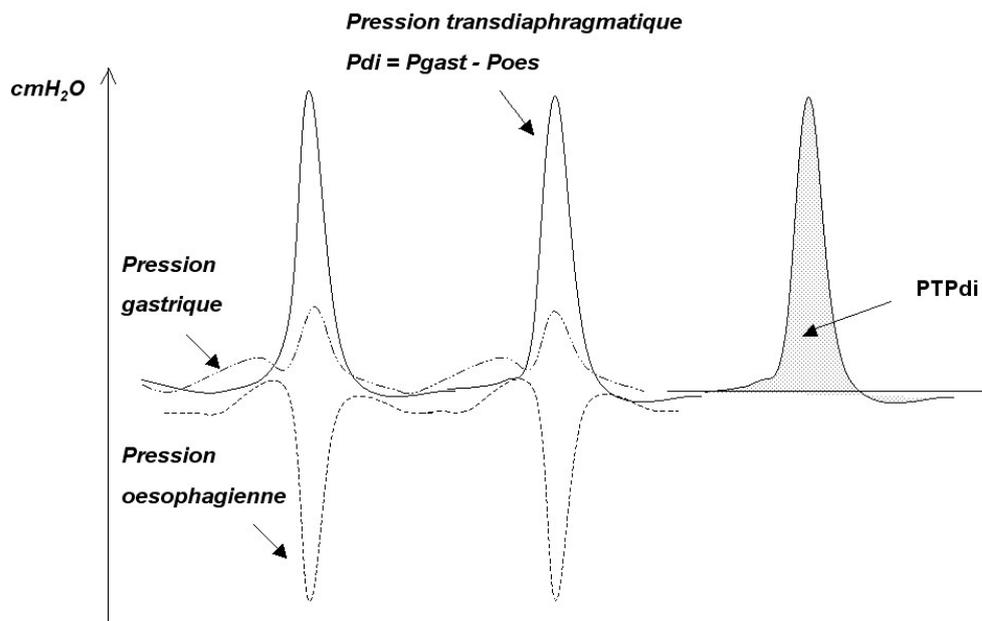
Ces limites ont conduit à développer d'autres indices pour quantifier l'effort musculaire respiratoire en réanimation, en particulier le *produit pression-temps* ou « *pressure time product* » appliqué à la pression pleurale (*PTP*) ou à la pression transdiaphragmatique (*PTPdi*).

La pression pleurale est approchée au moyen de la mesure de la pression œsophagienne (*Poes*) tandis que la pression gastrique est utilisée comme substitut de la pression régnant dans la cavité abdominale. La pression transdiaphragmatique est calculée comme la différence entre la pression gastrique (*Pgas*) et la pression œsophagienne (*Poes*) soit :

$$Pdi = Pgas - Poes \quad (\text{cmH}_2\text{O})$$

L'intégration de la courbe de pression oesophagienne (*PTP*) ou transdiaphragmatique (*PTPdi*) en fonction du temps et exprimée par cycle ou par minute offre à ce jour une des meilleures approches de l'effort des muscles respiratoires en ventilation mécanique (Cf. *Figure 5*). Mais cette technique nécessite un monitoring invasif par sonde à simple (pression oesophagienne) ou double ballonnet (pression trans-diaphragmatique) et n'est pas utilisée en pratique courante.

Figure 5 : Evaluation du travail respiratoire par calcul du *PTPdi* défini comme l'intégration de la courbe de Pression transdiaphragmatique (*Pdi*)



2 Agression du diaphragme en réanimation

2.1 L'agression musculaire en réanimation

Le séjour en réanimation est marqué par une atteinte neuro-musculaire fréquente (27) dont le mécanisme physiopathologique est multifactoriel et concerne à la fois le nerf et le muscle (28,29).

Cette atteinte est le plus souvent réversible, mais associée à une prolongation de la ventilation mécanique (30,31). Au sein de cette entité se démarque une atteinte qui semble plus spécifique des muscles respiratoires et plus particulièrement du diaphragme. La dysfonction diaphragmatique observée en réanimation apparaît secondaire des mécanismes complexes associant atrophie catabolique, mise au repos du muscle, efforts musculaires contrariés, agression septique et inflammatoire, désordres métaboliques et toxicité des médicaments notamment anesthésiques et sédatifs. Un des enjeux de la recherche sur le sujet est d'isoler et comprendre chaque facteur d'agression individuellement.

2.2 Dysfonction diaphragmatique en lien avec la ventilation mécanique

2.2.1 Dysfonction diaphragmatique induite par la décharge du système respiratoire

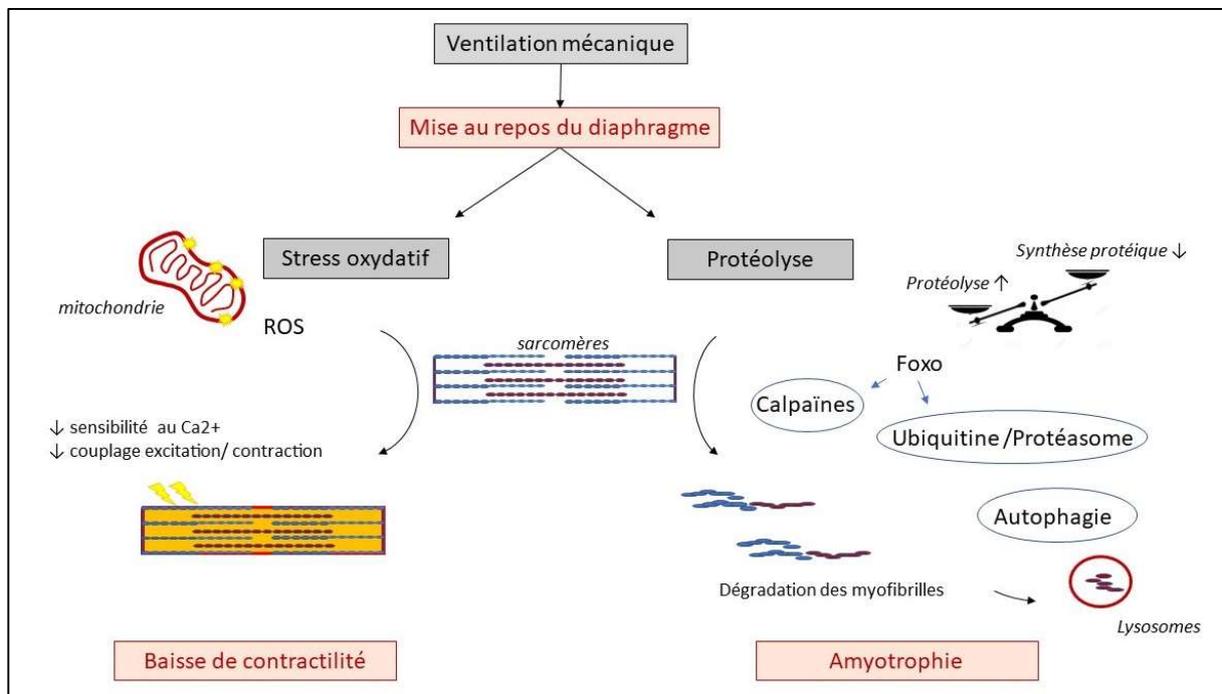
Il semble intuitif que la mise au repos d'un muscle se contractant habituellement 20.000 fois par jour conduise à son déconditionnement en quelques jours. La dysfonction diaphragmatique directement en lien avec la ventilation mécanique a d'abord été suspectée puis documentée sur des modèles animaux in vivo. Il a en effet été démontré qu'une ventilation mécanique contrôlée même de courte durée génère une baisse de 40 à 50% de la dépression produite par le diaphragme en réponse à une stimulation du nerf phrénique après 3 jours de ventilation mécanique chez le lapin (32), 5 jours chez le cochon (33) et 11 jours chez le babouin (34). Ces résultats ont été expliqués par une diminution intrinsèque de la contractilité des fibres musculaires grâce à des modèles d'analyses ex-vivo de diaphragme de rats exposés à la ventilation mécanique pendant 24-48h. (35,36). La dysfonction était d'autant plus importante que la ventilation était contrôlée (37) et n'était pas en lien avec la pression positive mais bien reliée à la mise au repos forcée du muscle respiratoire (32). Chez le rongeur, autant l'atteinte pouvait sembler précoce, autant elle apparaissait rapidement réversible avec la reprise d'une ventilation spontanée (38,39).

Chez l'humain, la mise en évidence d'une atteinte du diaphragme spécifiquement liée à la ventilation mécanique a été rendue difficile par la présence de nombreux facteurs intriqués (sepsis, médicaments, dénutrition, désordres métaboliques). Dès 1988 toutefois, l'observation autopsique de diaphragmes de nouveau-nés ventilés plus de 12 jours révélait une atrophie diffuse des fibres musculaires diaphragmatiques en comparaison avec celles d'enfants ventilés moins de 7 jours (40). Des arguments indirects étaient ensuite apportés par la mise en évidence d'une baisse de la pression produite par le diaphragme en réponse à une stimulation magnétique cervicale du nerf phrénique chez 33 patients (41). La preuve était finalement amenée 20 ans plus tard par Levine et al, dans un célèbre travail comparant les biopsies du diaphragme de 14 sujets donneurs d'organe à celles de 8 sujets opérés d'une intervention bénigne (42). Les donneurs étaient ventilés 18-69h alors que la ventilation était limitée à 2-3h dans le groupe contrôle. L'analyse montrait une atrophie significative des fibres musculaires lente et rapide ainsi que des signes de protéolyse et d'agression oxydante (42). Cette atteinte n'était pas retrouvée au niveau du muscle pectoral. Une seconde étude montée sur un design similaires a confirmé ces résultats et montré que l'atrophie était corrélée avec la durée d'exposition à la ventilation mécanique (43). Une durée d'exposition supérieure à 24h semblait toutefois nécessaire (43). L'intérêt de ces travaux est d'écarter toute interférence avec le sepsis.

Les mécanismes moléculaires à l'origine de l'atrophie semblent associer une augmentation de la protéolyse et du stress oxydatif (44,45) (*Cf Figure 6*). Le stress oxydatif conduit rapidement à une baisse de la sensibilité des myofibrilles au calcium et à une altération du couplage excitation/contraction de la fibre musculaire. La protéolyse intervient secondairement et pourrait en partie être médiée par le système ubiquitine/protéasome (46) sous l'activation soutenue des facteurs de transcription Foxo (47) et à une autophagie lysosomale. (48) On décrit également une protéolyse non lysosomale médiée par l'activation dérégulée du système des calpaïnes neutres. Les calpaïnes sont des protéases dépendantes du calcium qui clivent de nombreuses protéines, dont des protéines des myofibrilles (49). La ventilation mécanique prolongée semble activer les calpaïnes chez l'animal et chez l'homme (43,50) et de façon intéressante, l'inhibition des calpaïnes semble prévenir

l'apparition d'une dysfonction diaphragmatique induite par la ventilation (51). Le stress oxydatif est associé à une atteinte mitochondriale, également au premier plan (52,53). Des anomalies structurelles concordantes ont été décrites par analyse microscopique de fibres musculaires diaphragmatiques soumises à quelques jours de ventilation mécanique : lésions des myofibrilles, augmentation du nombre de vacuoles lipidiques dans le sarcoplasme et petites mitochondries anormales (32,54). Ces altérations pourraient conduire à un remodelage des fibres musculaires diaphragmatiques (44). Une altération de la sensibilité des myofibrilles au calcium a également été démontrée sur des biopsies humaines ex vivo, réversible après mise en présence d'un activateur de la troponine (55).

Figure 6. Mécanismes moléculaires de la dysfonction diaphragmatique induite par la ventilation mécanique



ROS, Reactive Oxygen Species (dérivés réactifs de l'oxygène) ; Foxo, Forkhead box O (protéines transcriptionnelles O se liant à l'ADN par leur domaine Forkhead).

2.2.2 Dysfonction diaphragmatique en lien avec la mise en charge excessive du système respiratoire

A l'inverse de la mise au repos, une contrainte excessive imposée au système respiratoire peut également conduire à une altération fonctionnelle et structurelle du diaphragme. Ainsi, l'augmentation artificielle des résistances trachéales chez le hamster entraîne une dégradation des myofibrilles diaphragmatiques (56). Cette destruction serait de mécanisme inflammatoire (56) et liée à une protéolyse médiée par les calpaïnes (57). Des indices de cette dysfonction diaphragmatique induite par un excès de charge inspiratoire existent également chez l'homme. Des volontaires sains soumis à une charge résistive excessive développent une baisse de leur contractilité diaphragmatique (58) et des biopsies de diaphragme de patients BPCO révèlent une dissociation des sarcomères d'autant plus importante que les sujets ont été soumis à une charge résistive élevée au préalable (59). Ces constats ouvrent l'hypothèse que le diaphragme puisse souffrir de façon significative lors d'une commande respiratoire excessive en regard d'une mécanique respiratoire altérée ou à l'occasion d'asynchronies patient-respirateur répétées (60).

2.3 Une dysfonction diaphragmatique induite par le sepsis ?

La mise en évidence d'un épuisement des muscles respiratoires immédiatement secondaire à une agression endotoxinique est démontrée chez le chien en ventilation spontanée (61) ou contrôlée (62) et chez le rongeur ventilé (63). Une baisse de la contractilité des fibres est alors associée à une diminution de l'activité musculaire électrique (63) sans qu'il soit possible de déterminer si l'inflammation ou l'hypotension sont responsables. En effet une dysfonction diaphragmatique par baisse de la pression de perfusion semble présente dans tout état de choc quelle que soit l'étiologie (64,65).

Une diminution de la force musculaire diaphragmatique maximale et de la capacité d'endurance musculaire a également été démontrée après sepsis prolongé à *Cocci Gram +* (66) et *Bacille Gram -*

(67,68) malgré l'absence d'hypotension associée. Les mêmes résultats étaient retrouvés sur des modèles expérimentaux de péritonite (69) ou de pancréatite (70).

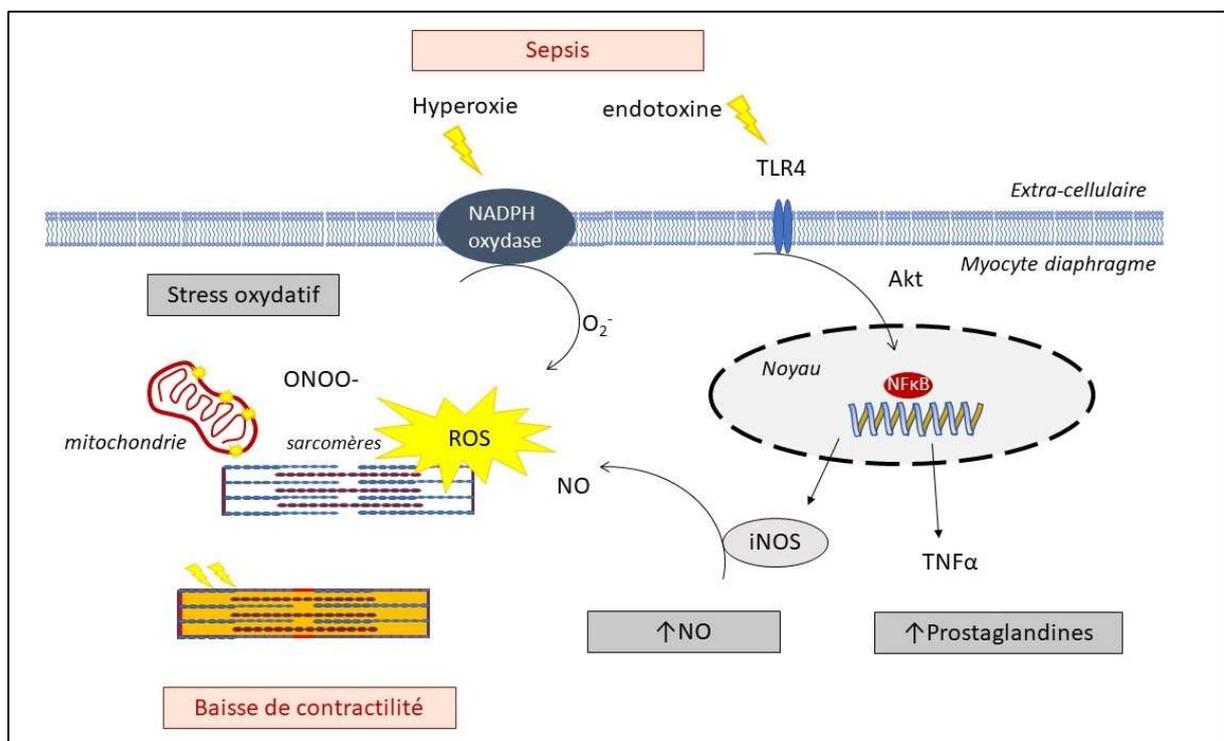
Les mécanismes physiopathologiques évoqués pour expliquer la dysfonction diaphragmatique secondaire au sepsis ont été schématisés en fonction du temps (71). A la phase initiale, on observerait une dette énergétique en lien avec l'altération de la microperfusion (72) et de l'extraction métabolique (73), malgré une redistribution du débit sanguin loco-régional vers le diaphragme actif (74). A la phase tardive, une atteinte secondaire et diffuse sur plusieurs jours serait quant à elle une conséquence directe de l'inflammation, médiée par ses protagonistes extra et intracellulaires : prostaglandines (75,76), cytokines (TNF α) (77), NF-kappa B (78), stress oxydatif (79) et production de NO (80) (Cf. Figure 7).

Une atteinte directe du diaphragme spécifiquement liée au sepsis chez l'homme a également été difficile à démontrer du fait des agressions intriquées. Des signes indirects ont été apportés par plusieurs travaux qui objectivaient une altération de la mécanique ventilatoire et un sevrage ventilatoire prolongé chez les patients septiques (31,81).

Dans un travail prospectif chez 85 patients de réanimation ventilés, Demoule et al ont mis en évidence que le sepsis était un facteur de risque indépendamment associé à une dysfonction diaphragmatique précoce (diagnostiquée par altération de la dépression trachéale en réponse à une stimulation cervicale [Pr, Stim < 11 cmH₂O]) dans les 24 premières heures suivant l'admission) (82). Étonnement, cette dysfonction diaphragmatique précoce semblait être un marqueur de gravité (associée à la mortalité et la durée de séjour), mais n'était pas un facteur de risque de sevrage prolongé. Une étude clinique scannographique a par ailleurs démontré que le volume du muscle était diminué de 29%, 25 jours après une admission en réanimation chez 14 patients septiques. En comparaison, ce volume était réduit de 11% chez 9 patients non septiques (83). L'atteinte du diaphragme était plus importante que celle d'un muscle de référence non impliqué dans la ventilation mécanique (psoas).

Une potentialisation des agressions ventilatoires et septique semble hautement probable, d'autant plus que les deux agressions partagent la voie d'activation intracellulaire médiée par les récepteurs TLR4 (84). La réunion de ces mécanismes physiopathologiques distincts mais intriqués conduit d'ailleurs certains auteurs à proposer aujourd'hui le terme de « faiblesse diaphragmatique liée aux soins intensifs ». (Critical illness-associated diaphragm weakness).

Figure 7. Mécanisme moléculaire de la dysfonction diaphragmatique induite par le sepsis



O_2^- , ion superoxyde ; ONOO-, ion peroxynitrite ; NO, monoxyde d'azote ; TLR4, Toll Like Receptor 4 ; Akt, protéine kinas B ; NFκB, Facteur nucléaire Kappa B ; TNFα, Facteur de nécrose tumorale α.

2.4 Autres facteurs d'agression diaphragmatique

En plus de la ventilation mécanique et du sepsis, d'autres facteurs semblent impliqués dans la survenue d'une dysfonction diaphragmatique en réanimation.

La sénescence pourrait jouer un rôle non négligeable : il a été montré que la contractilité diaphragmatique (pression transdiaphragmatique maximale) était significativement altérée par l'âge (85,86). Cette altération pourrait être expliquée par une diminution du pouvoir oxydatif et une augmentation de la proportion de fibres lentes (23).

Une étude translationnelle récente a testé l'hypothèse que l'altération de la fonction diaphragmatique pouvait être aggravée par l'application d'une pression expiratoire positive (PEP) excessive. La distension provoquée par la PEP entraînerait une atrophie longitudinale des myofibrilles en rapport avec une absorption des sarcomères. La faiblesse diaphragmatique serait démasquée lors de la reprise de la ventilation spontanée et la diminution de la PEP, les sarcomères n'ayant alors plus la taille optimale pour faire chevaucher efficacement les filaments d'actine et de myosine (87).

La chirurgie digestive haute et la chirurgie cardiaque sont des facteurs classiques de faiblesse diaphragmatique (88,89), probablement par altération de la conduction phrénique. L'utilisation de traitement sédatif concourt également clairement à diminuer la force diaphragmatique, qu'il s'agisse d'agents intraveineux (90,91) ou volatiles (92).

L'action des corticoïdes sur la fonction diaphragmatique des patients critiques est moins univoque et semble dépendre de la doses employée et de la durée d'exposition (93). De même, les curares pourraient avoir un effet variable selon le type de molécule utilisée (94,95).

L'action de l'hypercapnie semble également paradoxale. A court terme une hypercapnie aigüe provoque une baisse de la contractilité diaphragmatique (96). En revanche, l'exposition prolongée à l'hypercapnie pourrait exercer une action protectrice sur le diaphragme. Il a ainsi été démontré qu'une hypercapnie modérée (55-70 mm Hg) permettait de limiter la survenue d'une dysfonction diaphragmatique chez le cochon (97) et chez le rat (98) par diminution de la protéolyse et de l'inflammation (98). Toujours au plan métabolique, l'hypophosphorémie entraîne une diminution de la dépression diaphragmatique induite par une stimulation phrénique (99).

2.5 Prévalence de la dysfonction diaphragmatique en réanimation et implication sur le sevrage ventilatoire

Chez les patients de réanimation, la dysfonction du diaphragme est mise en évidence par la mesure d'une altération de la dépression trachéale secondaire à la stimulation cervicale magnétique du nerf phrénique (41,100). Une valeur inférieure à 11 cmH₂O est retenue comme valeur seuil de référence (82). Son incidence pourrait concerner jusqu'à 60% des patients (82,101) et sa présence est associée à une augmentation de la durée de ventilation mécanique ainsi qu'à une augmentation de la mortalité (82,102,103). Le dépistage de la dysfonction diaphragmatique fait ainsi aujourd'hui partie des algorithmes de prise en charge du sevrage des patients de réanimation (104,105).

Si la mise en évidence d'une dysfonction diaphragmatique au moment du sevrage ventilatoire apparaît un marqueur de gravité indéniable, aucune donnée concluante ne permet toutefois d'affirmer qu'il est possible de la prévenir ou la traiter efficacement chez l'homme. Plusieurs pistes font l'objet d'explorations.

2.6 Prévention de la dysfonction diaphragmatique

2.6.1 Traitements médicamenteux

Beaucoup d'études expérimentales médicamenteuses ont démontré une efficacité préventive sur l'apparition d'une dysfonction diaphragmatique chez l'animal : molécules anti-oxydantes (106), modulateurs de la protéolyse (107) ou sensibilisants des myofibrilles au calcium (55). Aucun de ces résultats n'a été reproduit chez l'homme pour l'heure.

2.6.2 Entraînement des muscles inspiratoires

L'entraînement quotidien des patients par l'application intermittente d'une charge résistive permet d'améliorer la performance musculaire (augmentation de la *P_Imax*) mais l'efficacité sur la

durée de sevrage est débattue, en particulier en raison de la difficulté à définir le groupe contrôle (108,109).

2.6.3 Maintien d'une ventilation spontanée

Il est bien démontré chez l'animal que le maintien d'une ventilation spontanée prévient la survenue d'une dysfonction diaphragmatique (37,110). Chez l'homme, l'atrophie semble d'autant plus importante que la ventilation est asservie, et semble réduite par le maintien d'une ventilation spontanée (60,111). La difficulté réside toutefois sur le choix du moment idéal pour lever la sédation et autoriser la ventilation libre. Les modes ventilatoires adaptés directement à la commande ventilatoire sont en théorie les plus adaptés mais n'ont pas fait la preuve d'une diminution de la durée du sevrage ventilatoire (112–114).

2.6.4 Stimulation électrique du diaphragme

Le maintien d'une contraction régulière du diaphragme par stimulation artificielle du nerf phrénique permet de prévenir la survenue d'une dysfonction diaphragmatique sur un modèle porcin. La stimulation est réalisée par le biais d'une électrode endovasculaire jugulaire (115). Des études humaines sont en cours pour valider le dispositif chez le volontaire sain (*Clinicaltrials.gov* NCT03107949) et explorer s'il permet de diminuer la durée de sevrage chez le patient de réanimation (*Clinicaltrials.gov* NCT03096639).

Pour évaluer l'ensemble de ces méthodes, des techniques d'explorations du diaphragme en routine clinique sont nécessaires.

3 Explorer le diaphragme d'un patient sous ventilation mécanique

L'évaluation de la fonction diaphragmatique en réanimation doit prendre en compte plusieurs contraintes. La première contrainte est liée à l'état de conscience du patient. Un certain nombre de

techniques nécessite en effet la participation active du patient et ne pourront être réalisées que chez un patient calme et coopérant, après arrêt de toute sédation. Par ailleurs, le clinicien a dû longtemps se satisfaire d'indices indirects qui ne sont pas spécifiques de la fonction musculaire diaphragmatique mais reflètent l'action de l'ensemble des muscles respiratoires. Enfin, les conditions de réalisation des tests en réanimation sont à l'origine d'une variabilité importante dont on ne pourra s'affranchir qu'en associant les tests (116). L'ensemble des techniques disponibles sont rassemblées dans les tables 1A et 1B.

Table 1. Méthodes cliniques d'appréciation de la force des muscles respiratoires

A. Méthodes nécessitant la coopération du patient

	Epreuve	Valeur seuil	Fonctions explorées	Limites
<i>P_{lmax}</i>	Pression inspiratoire maximale	H < -45 cmH ₂ O F < -30 cmH ₂ O	tous les muscles inspiratoires	interprétation difficile manque de spécificité
<i>P_{dmax}</i>	Pression transdiaphragmatique maximale	H < 40 cmH ₂ O F < 30 cmH ₂ O	diaphragme	invasif : nécessite une sonde à double ballonnet large gamme de valeurs utilité clinique limitée
<i>Sniff p_{di}</i>	Pression transdiaphragmatique pendant un sniff test	H < 100 cmH ₂ O F < 70 cmH ₂ O	diaphragme	invasif : nécessite une sonde à double ballonnet limitations techniques variabilité
<i>CPEF*</i>	Débit maximal à la toux	60l/min ?	muscles expiratoires	cut-off à définir

**CPEF, Cough peak expiratory flow.*

B. Méthodes ne nécessitant pas la coopération du patient

	Epreuve	Valeur seuil	Fonctions explorées	Limites
<i>PO.1</i>	Pression d'occlusion	< 3 cm H ₂ O	commande transmission tous les muscles inspiratoires	indice composite sous-estime l'effort si hyperinflation dynamique
<i>Eadi</i>	Electromyogramme	?	diaphragme	Invasif : nécessite une sonde spécifique Variabilité
<i>Ptr, stim</i>	Pression trachéale après stimulation phrénique	< 11 cmH ₂ O	diaphragme	invasif et inconfortable pour le patient nécessite la compétence technique et le matériel

- **La pression inspiratoire maximale statique (*P_Imax*)** reflète l'effet de l'ensemble des muscles inspiratoires. Sa mesure nécessite la réalisation d'un effort inspiratoire maximal, voies aériennes fermées et sa valeur est donc proportionnelle à l'effort du patient, dont elle implique une coopération importante. La technique la plus simple chez le patient intubé est de lui demander de réaliser une inspiration statique contre occlusion pendant une seconde. L'utilisation supplémentaire d'une valve unidirectionnelle permet de faire précéder la manœuvre d'une expiration amenant le patient proche de son volume résiduel. Malgré cette stratégie qui vise à standardiser la technique (117), les valeurs mesurées chez le patient intubé sont peu reproductibles et souvent sous-estimées (118,119). Une valeur < -80 cmH₂O permet toutefois d'exclure une faiblesse respiratoire importante (21).

- **La pression transdiaphragmatique (*P_{di}*)** nécessite l'insertion d'une sonde à double ballonnet (œsophagien et gastrique) et correspond à la somme des valeurs absolues des deux valeurs (cf. supra). Comme la pression transdiaphragmatique représente la pression développée par le diaphragme, sa valeur doit idéalement être rapportée au volume courant pour déterminer son rendement. (120) Ainsi la *P_{di}* a été proposée pour titrer le niveau d'aide inspiratoire. (121) A partir de ce monitoring, il est également possible de mesurer une *P_{di}* maximale ou une *P_{di}* au cours d'un sniff

test. Ces deux épreuves nécessitent toutefois la coopération du patient et ne seront pas réalisables en cas de sédation.

- **Le débit maximal mesuré pendant une épreuve de toux** est également une mesure relativement simple à obtenir en réanimation chez un patient ventilé. Plusieurs travaux ont retrouvé que l'altération de cet indice était corrélée à un mauvais pronostic de l'extubation, avec toutefois une grande disparité de seuil (122–124). De plus, la force de toux n'est pas (ou très peu) déterminée par le diaphragme et dépend surtout des muscles expiratoires.

- **La pression d'occlusion (PO.1)** est la pression développée 100 ms après le début d'une inspiration. Chez le patient intubé, la mesure est réalisée au décours d'une courte occlusion précédant l'ouverture de la valve inspiratoire. Cet indice est le témoin de l'intensité de la commande ventilatoire centrale (125), mais dépend de nombreux paramètres : intégrité des voies de conduction nerveuses, couplage électromécanique, force musculaire inspiratoire, et vitesse de contraction. Une PO.1 élevée correspond toujours à une augmentation de l'activité des centres respiratoires, mais l'inverse ne peut être inféré. En cas d'hyperinflation dynamique, la PO.1 sous-estime la commande centrale (126).

- **L'électromyographie du diaphragme (EMG)** peut être réalisée par 3 voies d'abord distinctes : percutanée, transcutanée et œsophagienne. La méthode percutanée de surface est la plus simple. Le signal est obtenu par le biais d'électrodes adhésives positionnées en regard de l'insertion costale du diaphragme. La technique peut-être utile pour détecter le début et la fin de la contraction diaphragmatique et ainsi repérer les asynchronies patient-respirateur (127–129). Cette technique non invasive est toutefois peu spécifique du diaphragme car le signal peut être parasité par l'activité électrique de muscles extra-respiratoires (21). Elle est peu fiable en réanimation. L'utilisation d'aiguilles percutanées permet d'améliorer la spécificité de la technique mais expose le patient au risque de pneumothorax et/ou de plaies hépatiques et spléniques. Plus récemment, la possibilité d'obtenir un signal EMG du diaphragme crural par le biais d'électrodes œsophagiennes a permis

d'obtenir un monitoring fiable du signal diaphragmatique de façon continue (Eadi), et ainsi de développer des modes ventilatoires asservis à la commande diaphragmatique (112). L'Eadi est proposé pour évaluer l'effort inspiratoire (130), titrer le niveau d'assistance ventilatoire (131) ou évaluer les interactions patient-ventilateur (132,133), mais nécessite l'insertion d'une sonde œsophagienne spécifique. Il n'y a pas de valeur seuil permettant de définir une altération de la force diaphragmatique.

- La mesure de la variation de pression trachéale générée par une stimulation du nerf phrénique (*Ptr, stim*) constitue aujourd'hui la technique de référence en réanimation. Elle permet de standardiser une évaluation de la force développée par le diaphragme quel que soit le niveau de sédation et de coopération du patient. Elle est spécifique du diaphragme. La variation de pression trachéale générée par une stimulation standardisée est en effet très bien corrélée à la variation de pression œsophagienne pour la même stimulation (134). La stimulation électrique (qui permettait de stimuler spécifiquement le nerf phrénique) a été remplacée par la stimulation magnétique antérieure, moins douloureuse et bien plus accessible en réanimation (135,136). La technique nécessite toutefois un matériel dédié et une expertise qui la relègue pour l'heure exclusivement au cadre de la recherche clinique. Cette technique constitue toutefois le gold standard pour dépister une dysfonction du diaphragme en réanimation (82,101).

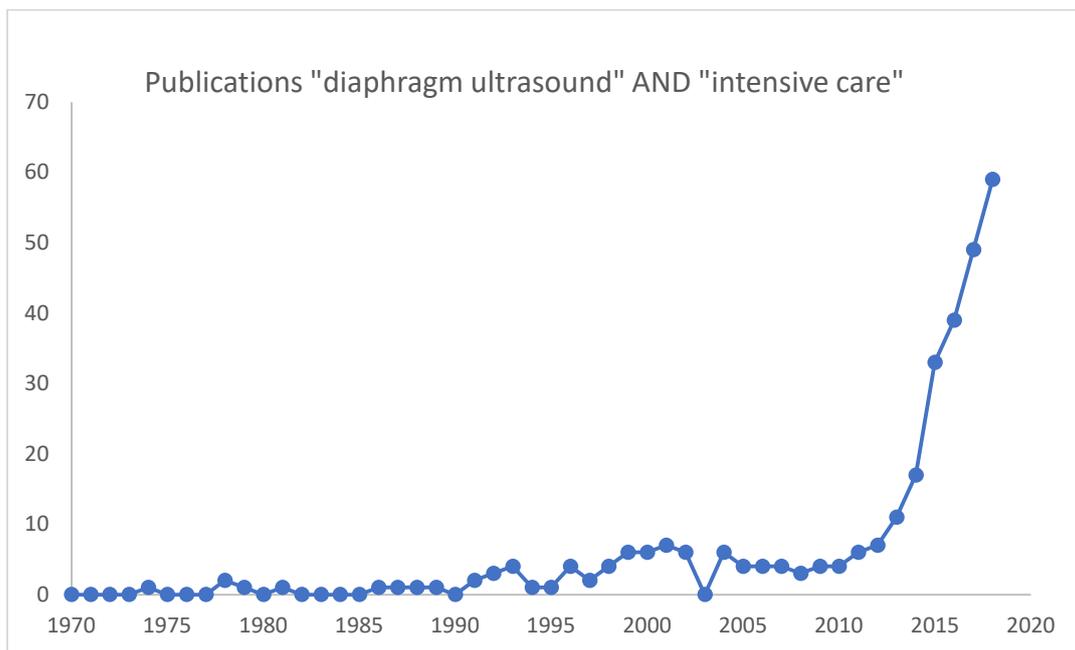
4 Echographie du diaphragme

L'échographie du diaphragme fait l'objet d'un engouement en réanimation depuis une dizaine d'années (Cf. *Figure 8*). L'accessibilité et la simplicité de la technique en ont fait une technique d'étude facile pour appréhender le comportement du principal muscle respiratoire. Cet intérêt n'a fait que se renforcer avec l'amélioration des performances des appareils, des sondes et des logiciels de traitement d'image. Cependant, cette technique ne peut se pratiquer sans intégrer un certain nombre de limites.

Comme tout muscle squelettique, le diaphragme est très peu échogène en soi. Son identification est toutefois permise par ses rapports anatomiques directs. En effet, il est tapissé de chaque côté par des séreuses hyperéchogènes : dans sa partie thoracique, par la plèvre pariétale et dans sa partie abdominale par le feuillet péritonéal. Ces structures apparaissent brillantes et sont facilement identifiables. L'observation de la coupole diaphragmatique tendineuse en profondeur et de la zone d'apposition musculaire au niveau du gril costal font appel à des techniques et des sondes d'échographie aux propriétés très différentes.

Figure 8. Publications sur l'échographie du diaphragme en réanimation

Nombre de publications annuelles recensées sur la base documentaire Medline en croisant « diaphragm ultrasound » et « intensive care »



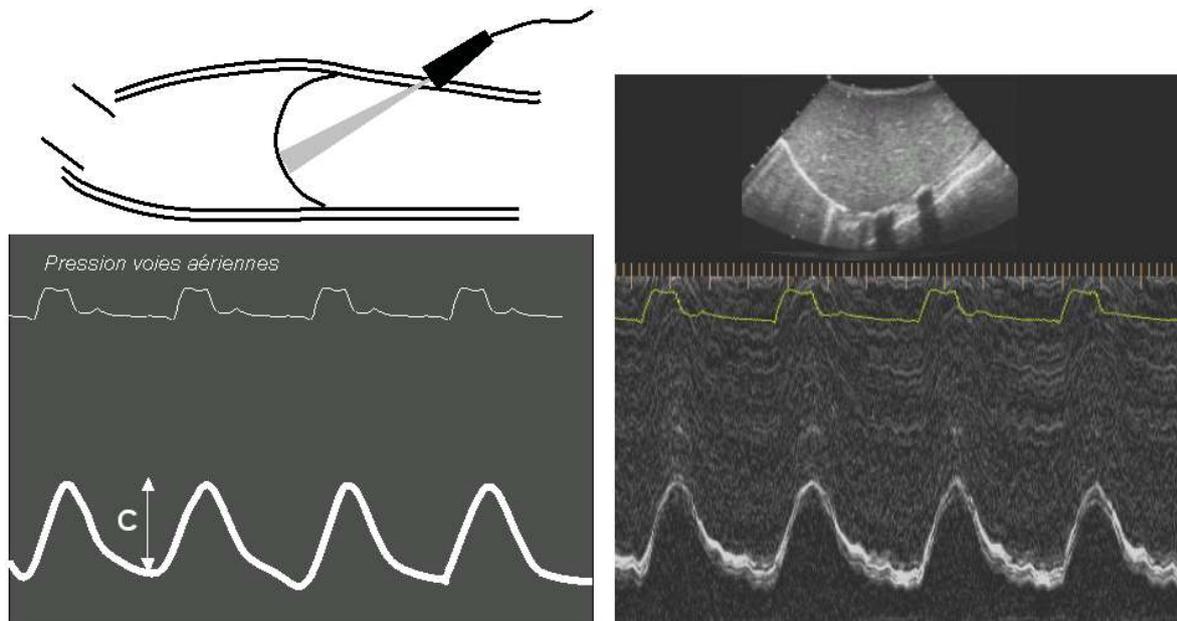
4.1 Excursion de la coupole

Une première approche des mouvements diaphragmatiques est possible avec une sonde de faible fréquence (≤ 5 MHz) ayant une forte pénétration et une résolution moyenne (sonde

abdominale ou sonde d'échocardiographie). La sonde est positionnée sur la partie supérieure de l'abdomen, 1 à 2 cms en dessous du dernier arc costal et au niveau de la ligne médio-claviculaire puis dirigée vers la coupole dans une direction apicale, légèrement vers l'arrière. La visualisation des coupoles (la droite étant souvent mieux vue que la gauche) permet l'enregistrement en mode temps mouvement (TM) de l'excursion cranio-caudale du dôme postérieur, également appelée course diaphragmatique [C] (*Cf. Figure 9*). Lorsque l'image est inaccessible par la voie sous-costale, il est possible d'utiliser la voie latérale (ligne axillaire médiane), puis d'appliquer une correction d'angle par méthode de TM anatomique (137).

La valeur de l'excursion est directement corrélée au volume mobilisé (138). Les valeurs normales de l'excursion diaphragmatique chez le sujet sain en ventilation calme, inspiration profonde et inspiration forcée sont respectivement de 18 (± 3) mm, 70 (± 11) mm et 29 (± 6) mm chez l'homme et de 16 (± 3) mm, 57 (± 10) mm et 26 (± 5) mm chez la femme (139). Une excursion inférieure à 25 mm à l'inspiration maximale définit une dysfonction diaphragmatique (140). Ce seuil a été validé en réanimation pour détecter des dysfonctions diaphragmatiques survenues après chirurgie cardiaque (140). Par ailleurs, une dysfonction diaphragmatique définie par une altération de l'excursion (< 10 mm en ventilation spontanée) a été décrite comme associée à un risque accru d'échec du sevrage de la ventilation mécanique en réanimation polyvalente (141) et à une surmortalité (142).

Figure 9 : Enregistrement de « l'excursion » ou « course diaphragmatique (C) » en mode TM



4.2 Epaisseur de la zone d'apposition

Une analyse plus fine de l'activité musculaire diaphragmatique est rendue possible par les sondes d'échographies à faible pénétration mais haute résolution. L'emploi d'une sonde de fréquence ≥ 10 MHz permet en effet l'observation du diaphragme là où il s'appose contre la paroi de la cage thoracique au niveau des 8-11^{èmes} côtes environ (Cf. Figure 10). A cet endroit, appelé « zone d'apposition », l'épaisseur du diaphragme peut être mesurée avec précision en mode 2D. L'examen est réalisé en position demi-assise en positionnant la sonde sur la ligne axillaire moyenne. Le faisceau d'ultrasons est dirigé perpendiculairement au diaphragme. L'image droite est souvent de meilleure qualité que la gauche, du fait de l'échogénicité du parenchyme hépatique sous-jacent. La zone d'apposition peut être identifiée 0,5 à 2 cm au-dessous du cul de sac pleural. Ce dernier est repéré grâce à l'interposition cyclique de l'artéfact aérique inspiratoire entre la sonde et le parenchyme sous-jacent (foie et diaphragme). Le diaphragme est repéré entre deux lignes brillantes hyperéchogènes, écho des séreuses pleurale et péritonéale (Cf. Figure 11). Une troisième ligne

hyperéchogène médiane est parfois observée et pourrait correspondre à une structure tendineuse ou vasculo-nerveuse (143,144).

Une acquisition en mode TM permet de mesurer l'épaisseur comme la distance séparant les deux lignes. Cette mesure a été validée par des études post-mortem sur une série autopsique (145). L'épaisseur du diaphragme est très variable d'un sujet à l'autre et dépend du poids et du statut nutritionnel (26). Les valeurs normales varient de 1,7 à 3 mm (144,146). On retient une valeur moyenne de $1,9 \pm 0,4$ mm chez l'homme et $1,4 \pm 0,3$ mm chez la femme (147). Le marquage cutané de la zone d'enregistrement permet d'améliorer nettement la reproductibilité ainsi que la répétabilité de la mesure lorsqu'elle est répétée plusieurs jours de suite (148).

La technique a été proposée pour repérer une pseudo-hypertrophie diaphragmatique lors de la myopathie de Duchenne (149) ou suivre l'altération de la fonction ventilatoire chez les patients présentant une sclérose latérale amyotrophique (150). En réanimation, l'apparition d'une atrophie diaphragmatique peut ainsi être détectée par cette technique dès les premiers jours de ventilation mécanique (60,148,151–153).

Figure 10 : Positionnement de la sonde d'échographie haute fréquence au niveau de la zone d'apposition.

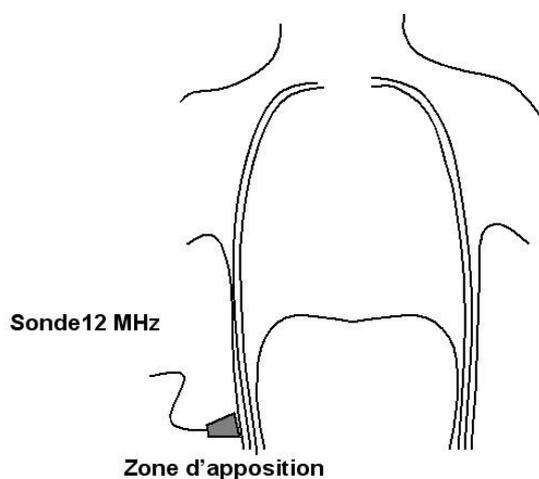
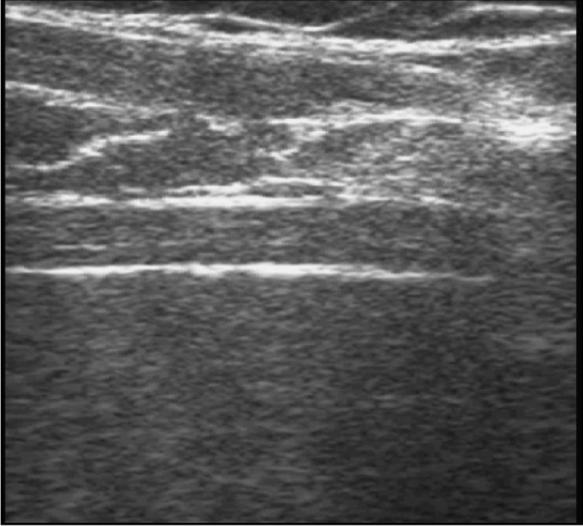
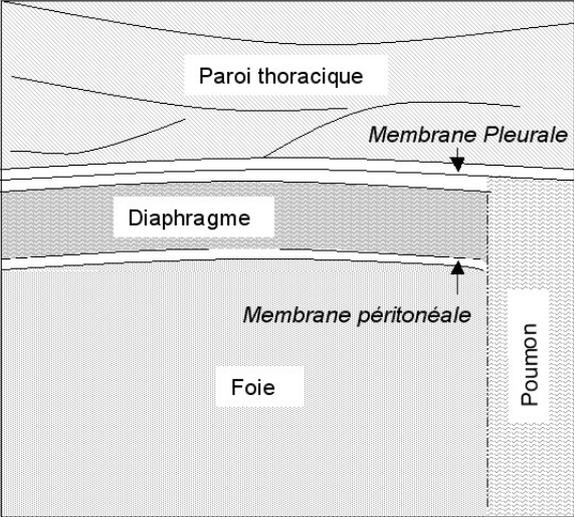


Figure 11 : Coupe 2D du diaphragme au niveau de la zone d'apposition

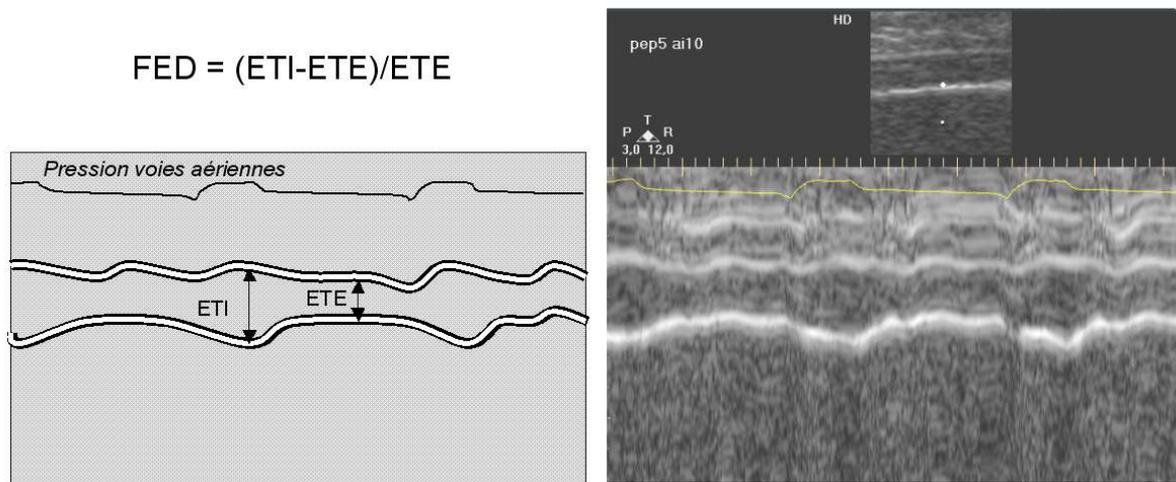


4.3 Epaissement de la zone d'apposition

Au niveau de la zone d'apposition, une variation très nette de l'épaisseur du muscle au cours du cycle respiratoire est observable et correspond à la contraction des fibres musculaires de la portion costale. Le volume d'un muscle étant constant, l'épaisseur diaphragmatique devrait être inversement proportionnelle à la réduction de sa longueur. Cependant la partie centrale du diaphragme est plus pauvre en fibres musculaires (centre tendineux) et il existe une accentuation de l'épaississement dans les zones d'insertions costales latérales et antérieures (6). La mesure échographique de la variation d'épaisseur (appelée fraction d'épaississement diaphragmatique, *FED*) durant la contraction musculaire est possible en mode TM. Les mesures sont réalisées en fin d'inspiration (*ETI* : épaisseur télé-inspiratoire) et en fin d'expiration (*ETE* : épaisseur télé-expiratoire), les cycles respiratoires étant repérés à l'aide de la courbe de pression des voies aériennes affichée sur l'échographe. La fraction d'épaississement du diaphragme est calculée selon la formule $FED = (ETI - ETE) / ETE$ et exprimée en pourcentage (Cf. Figure 12).

Il existe une corrélation entre la *FED* et le volume courant lors de la ventilation spontanée chez des sujets sains (145). Par ailleurs, on retrouve une association entre *FED* et effort inspiratoire lorsqu'on demande à des sujets sains de faire des épreuves d'inspiration maximales (épreuve de sniff test ou pression inspiratoire maximale) (154). Une anesthésie accidentelle du nerf phrénique entraîne une disparition de l'épaississement (155). La paralysie diaphragmatique est caractérisée par une quasi-absence d'épaississement ($FED < 20\%$), voire un amincissement paradoxal lors de l'inspiration (156). Chez des patients présentant une paralysie diaphragmatique, le suivi échographique de l'épaississement du diaphragme sur plusieurs mois permet de suivre la récupération de la fonction respiratoire. L'augmentation progressive de l'épaississement est corrélée à l'amélioration de la capacité vitale, de la pression inspiratoire maximale et à l'épaisseur du muscle (157).

Figure 12 : Déroulement en mode TM et calcul de la fraction d'épaississement du diaphragme (FED : fraction d'épaississement du diaphragme, ETE : épaisseur télé-expiratoire, ETI : épaisseur télé-inspiratoire)



4.4 Doppler tissulaire

La technique de doppler tissulaire (*TDI*) s'est largement développée en échocardiographie pour étudier spécifiquement la vitesse tissulaire des parois ventriculaires cardiaques (158,159). Son application aux muscles respiratoires apparait donc cohérente. Une première étude (hors réanimation) chez des sujets sains et des patients porteurs de neuromyopathie montre une bonne corrélation entre la mesure du *TDI* au niveau de la coupole droite au cours d'un sniff test et la capacité vitale forcée (160). Une étude chez des nouveau-nés ventilés montre par ailleurs une excellente reproductibilité (161). Ces données incitent à poursuivre les investigations concernant cette technique.

4.5 Technique de speckle tracking

L'imagerie de 2D-strain est également une technologie qui provient de l'échocardiographie. Il s'agit d'un outil de détection automatisée du déplacement de marqueurs acoustiques naturels : *les speckles*. Ces *speckles* sont naturellement présents au sein de l'imagerie échographique. Leur déplacement est ainsi suivi pendant un cycle (battement cardiaque ou cycle respiratoire par exemple) jusqu'à leur retour à leur position initiale. Le déplacement spatial de l'ensemble des *speckles* permet de construire une représentation géométrique fidèle du déplacement tissulaire local. La moyenne de l'ensemble de la déformation permet de calculer un *strain*, qui représente la déformation maximale d'un tissu par rapport à son état basal et un *strain rate* qui correspond à sa vitesse de déformation. Cette technique a été appliquée avec succès au diaphragme de 13 volontaires sains dans un premier travail (162). Le *strain* et le *strain rate* étaient bien corrélés à la pression transdiaphragmatique. Un autre travail chez des volontaires sains a utilisé cette technique pour démontrer que la déformation du diaphragme lors d'un effort soutenu était maximale au niveau de la zone d'apposition par rapport au diaphragme crural (163).

II. Démarche scientifique et conduite de la thèse

1. Position du problème

L'agression du diaphragme et de l'ensemble des muscles respiratoires en réanimation est un processus silencieux mais fréquent chez le patient ventilé. Si les facteurs d'agression sont multiples, la responsabilité directe de la ventilation mécanique apparaît prépondérante et permet de positionner la dysfonction diaphragmatique parmi les effets collatéraux indésirables de l'assistance ventilatoire. Ses conséquences sur le pronostic vital, le sevrage de la ventilation mais aussi la réhabilitation post-réanimation en font un sujet d'intérêt majeur à tous les stades de la prise en charge ventilatoire : conduite de la ventilation non-invasive, décision d'intubation, gestion de la sédation, choix du mode ventilatoire et décision d'extubation. Les enjeux pour le réanimateur sont de plusieurs natures : identifier et quantifier la dysfonction diaphragmatique, pour idéalement la prévenir ou la traiter.

Une telle ambition nécessite cependant de pouvoir explorer directement le muscle diaphragmatique au lit du malade, avec des outils simples, robustes et reproductibles. La technique idéale devrait permettre d'appréhender la morphologie et la trophicité du muscle, mais aussi son mouvement, sa fonctionnalité, sa puissance et son rendement. La technique se doit d'être disponible au lit du malade pour prendre en compte la variabilité du comportement ventilatoire à tout moment, en fonction des conditions de charge immédiates et idéalement permettre un monitoring.

L'objet de la thèse est de situer l'intérêt clinique de l'échographie du diaphragme dans ce contexte et de positionner cet outil parmi les différentes méthodes disponibles pour appréhender la fonction diaphragmatique en réanimation. Les techniques échographiques bénéficient d'améliorations technologiques régulières, en particulier concernant la définition des images. Par ailleurs, la diffusion matérielle et pédagogique de l'échographie en réanimation au cours des 20 dernières années en a fait une technique particulièrement accessible au lit du malade. Il apparaissait

fondamental de cerner les apports mais aussi les limites de l'échographie du diaphragme avec une méthodologie rigoureuse.

2. Objectifs du travail

Les objectifs de cette thèse sont à la fois orientés vers la compréhension fondamentale et vers la finalité clinique. Ils comportent les aspects suivants :

- Comprendre la signification physiologique de l'épaississement échographique du diaphragme tel qu'il est mesuré au niveau de la zone d'apposition ; et déterminer si la mesure de la fraction d'épaississement peut être utilisée en clinique comme reflet du travail musculaire diaphragmatique.
- Déterminer si l'échographie du diaphragme permet d'objectiver l'atrophie du diaphragme dans les premiers jours de ventilation mécanique au niveau de la zone d'apposition. Si oui, caractériser les déterminants d'une telle atrophie et la comparer à l'atrophie musculaire périphérique.
- Déterminer si la réalisation d'une échographie diaphragmatique est utile dans le processus de décision d'extubation chez des patients à haut risque d'échec d'extubation.
- Décrire et tester une technique couplant échographie continue du diaphragme et courbes de pression des voies aériennes pour dépister et caractériser les asynchronies patient-ventilateur.

3. Hypothèses

Un *travail préliminaire* a exploré si l'observation de l'épaississement du diaphragme au niveau de la zone d'apposition était possible et reproductible chez des patients de réanimation. L'objectif était de déterminer si la fraction d'épaississement était corrélée au travail diaphragmatique mesuré par la technique de référence, à savoir l'intégrale de la mesure de la pression transdiaphragmatique

(produit pression temps *PTPdi*). Douze patients ont ainsi été enregistrés en ventilation non invasive (VNI) immédiatement après extubation à différents niveaux de pression d'aide inspiratoire, afin de faire varier le niveau de mise en charge du système respiratoire. Ce travail a objectivé une corrélation entre fraction d'épaississement et *PTPdi*, mais révélait une importante variabilité intra et interindividuelle de la technique. Ce travail encourageant a conduit à poursuivre les investigations autour de la pertinence clinique de l'échographie et posé les fondements du travail de thèse présenté ici, qui s'articule autour de 4 hypothèses :

La *première hypothèse* était que la fraction d'épaississement ait une variabilité à la fois intrinsèque (liée à la technique de recueil), mais également extrinsèque (influence de facteurs liés aux comorbidités, à la prise en charge en réanimation, et aux conditions de charges respiratoires). Pour répondre à cette hypothèse, un premier travail a caractérisé précisément les déterminants de la fraction d'épaississement, par le biais d'une étude ancillaire d'un essai sur le sevrage de la ventilation mécanique (étude BMW). La fraction d'épaississement a été mesurée prospectivement chez 55 des patients à l'initiation du sevrage ventilatoire. Ce travail a également exploré si la fraction d'épaississement était davantage altérée en présence d'une neuromyopathie de réanimation clinique, afin de tester l'hypothèse qu'agression musculaire diaphragmatique et périphérique étaient des processus au moins partiellement distincts.

Une *seconde hypothèse* était que l'atrophie diaphragmatique induite par la ventilation mécanique pouvait être observée et quantifiée par la mesure répétée de l'épaisseur du diaphragme au niveau de la zone d'apposition. Pour tester cette hypothèse, la zone d'apposition de 28 patients a été mesurée entre J1 et J5. Cette mesure a été comparée d'une part à l'épaisseur d'un muscle extra-respiratoire (pectoral) et d'autre part à l'épaisseur du diaphragme de 7 sujets non ventilés.

Une *troisième hypothèse* était que la mesure de l'excursion ou de l'épaississement du diaphragme en ventilation spontanée avant l'extubation permettait de dépister une dysfonction diaphragmatique à risque d'échec d'extubation. Cette hypothèse a conduit à réaliser un travail multicentrique chez 191

patients sélectionnés en raison de l'existence d'un risque élevé d'échec d'extubation. Ce travail a précisé la problématique de l'impact de la dysfonction diaphragmatique sur l'extubation proprement dite, une fois l'épreuve de sevrage réussie.

La *quatrième hypothèse* était que l'implémentation des courbes de pression des voies aériennes sur le défilement temps mouvement des signaux diaphragmatiques (épaississement ou excursion) permettait de dépister et caractériser efficacement les asynchronies patient-ventilateur. Cette hypothèse a été testée chez 15 volontaires sains soumis à une ventilation non invasive avec fuites artificielles contrôlées dans le but de recréer expérimentalement les principales asynchronies en VNI, à savoir les auto-déclenchements et les insufflations prolongées.

III. Travaux réalisés

Prologue

*Diaphragm ultrasonography to estimate the work of breathing during
non-invasive ventilation*

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Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation

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Electronic supplementary material

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Abstract Purpose: Ultrasonography allows the direct observation of the diaphragm. Its thickness variation measured in the zone of apposition has been previously used to diagnose diaphragm paralysis. We assessed the feasibility and accuracy of this method to assess diaphragmatic function and its contribution to respiratory workload in critically ill patients under non-invasive ventilation. **Methods:** This was a preliminary physiological study in the intensive care unit of a university hospital. Twelve patients requiring planned non-invasive ventilation after extubation were studied while spontaneously breathing and during non-invasive ventilation at three levels of pressure support (5, 10 and 15 cmH₂O). Diaphragm thickness

was measured in the zone of apposition during tidal ventilation and the thickening fraction (TF) was calculated as (thickness at inspiration – thickness at expiration)/thickness at expiration. Diaphragmatic pressure–time product per breath (PTP_{di}) was measured from oesophageal and gastric pressure recordings.

Results: PTP_{di} and TF both decreased as the level of pressure support increased. A significant correlation was found between PTP_{di} and TF ($\rho = 0.74$, $p < 0.001$). The overall reproducibility of TF assessment was good but the coefficient of repeatability reached 18 % for inter-observer reproducibility. **Conclusions:** Ultrasonographic assessment of the diaphragm TF is a non-invasive method that may prove useful in evaluating diaphragmatic function and its contribution to respiratory workload in intensive care unit patients.

Keywords Ultrasound · Diaphragm · Ventilation

Introduction

Work of breathing is a central physiologic parameter in the assessment of a critically ill patient's respiratory function [1]. The diaphragm is the main respiratory

muscle and plays a central role in the pathophysiology of respiratory failure [2]. Evidence for ventilator-induced diaphragmatic dysfunction is now well established in animal models [3–5] and in critically ill patients [6–8]. On the other hand, optimal setting of the ventilator should

theoretically target a clinically acceptable level of work of breathing. Most assisted modes of ventilation have been studied regarding their ability to reduce the work of breathing, especially during weaning from mechanical ventilation or non-invasive ventilation (NIV) [9, 10]. Several methods have been used in the clinical research setting in critically ill patients to assess diaphragmatic function, including diaphragm electromyography, measurement of pleural (or oesophageal) and gastric pressures and derived variables (work of breathing) [11]. This highlights the need for simple and accurate methods to assess diaphragmatic performance in the intensive care unit (ICU) setting. Ultrasonographic-based determination of diaphragm excursions may help identify patients with diaphragmatic dysfunction during weaning from mechanical ventilation [12–14]. Ultrasonography also allows direct visualization of the diaphragm's thickness in its zone of apposition. Measurement of the thickening of this muscle segment was described back in 1989 [15] and has been used to assess diaphragm contraction in healthy subjects or to diagnose diaphragm paralysis [16]. We hypothesized that this measurement could reflect the magnitude of diaphragmatic work and could help clinicians to optimize ventilator settings. Because pressure support ventilation is known to reduce the work of breathing, the relationship between TF and the level of pressure support was of special interest. However, the accuracy and feasibility of this method have not been evaluated in ICU patients to date. The purpose of our study was to determine whether the assessment of diaphragm thickening in its zone of apposition could be feasible, accurate and reliable in critically ill patients and to assess its usefulness as an index of respiratory workload under NIV.

Methods

Patient selection

Patients intubated for 48 h or more, who tolerated a 1 h spontaneous breathing (SB) trial after recovery from their acute disease [9], were extubated and considered eligible for the study. Patients at high risk of respiratory distress requiring early NIV after extubation were enrolled if they had at least two of the following risk factors for respiratory failure after extubation: age older than 65 years, chronic obstructive pulmonary disease (COPD) or other type of chronic respiratory failure, heart failure as a cause for intubation, and an Acute Physiology and Chronic Health Evaluation [17] (APACHE) II score greater than 12 on the day of extubation [18, 19]. Exclusion criteria were as follows: tracheostomy, age younger than 18 years, head trauma or surgery, recent gastric or oesophageal surgery, active upper gastrointestinal bleeding, excessive amount

of respiratory secretions, poor cooperation, and decision to limit life-supporting treatments in the ICU. All included patients gave their informed consent to participate in the study, which was approved by the appropriate ethics committee (Comité de Protection des Personnes, Ile de France IX, approval number 05-025).

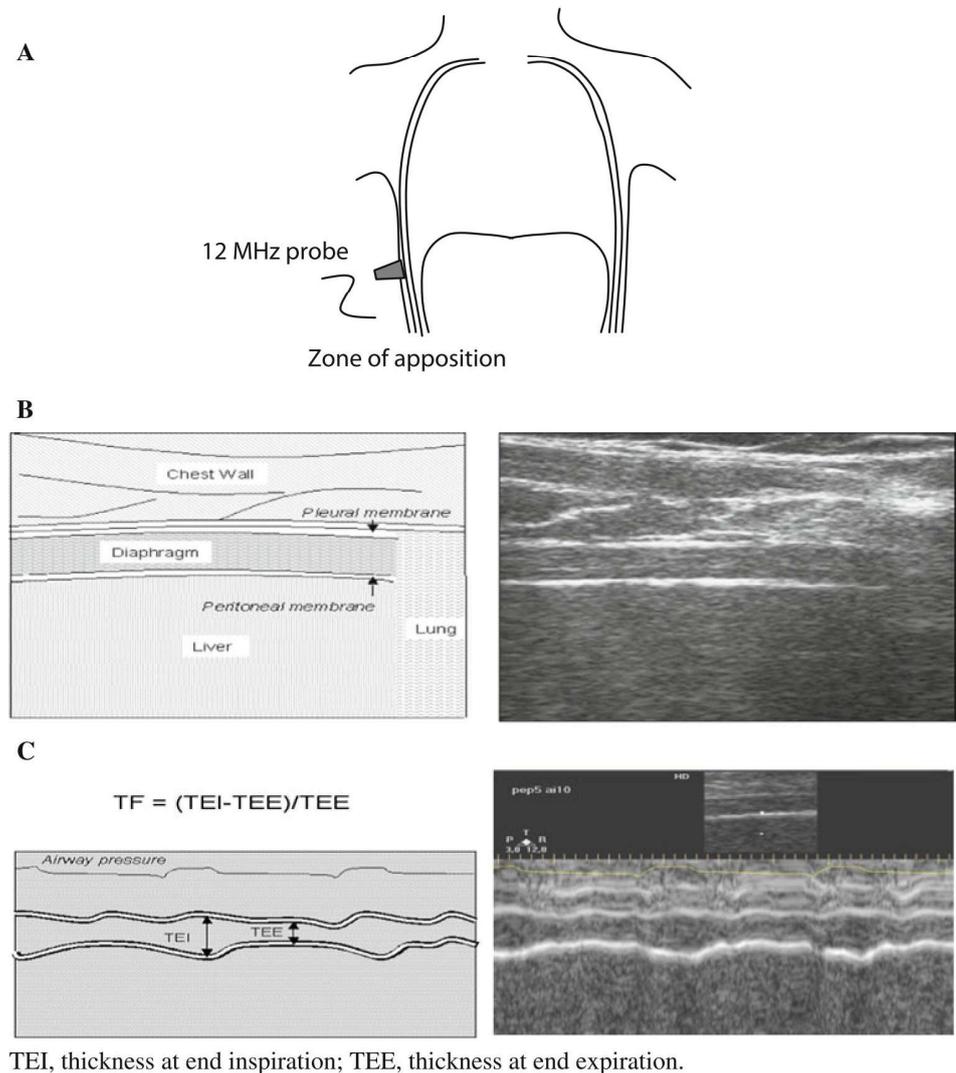
NIV

NIV was applied via a standard ICU ventilator (the type depending on availability), with an oronasal mask, in pressure support (PS) mode, as per the standard procedure in our unit. Baseline measurements were performed during SB. Recordings were then obtained during three NIV periods (with 5, 10 and 15 cmH₂O of PS level), in random order. Positive end-expiratory pressure (PEEP) was maintained at 5 cmH₂O and the inspired oxygen fraction was kept constant throughout the three NIV periods. Each of these three periods, as well as the SB period, lasted about 15 min. Pressure and flow data were recorded during the last 5 min of each condition after 5–10 min with a stable breathing pattern. The ultrasound examination was performed concomitantly.

Ultrasonography

The patients were studied in the semi-recumbent position throughout the study. Ultrasonography was performed by two intensivists both experienced in ultrasonography, using an Envisor system (Philips Ultrasound, Bothell, WA) equipped with a high resolution 12 MHz ultrasound linear probe. Using the signal from the ventilator, airway pressure was displayed on the screen of the Echo-Doppler machine during NIV, ensuring accurate determination of the tracings relative to the respiratory cycle. Ultrasound recordings of diaphragm thickness were performed as previously reported [15]. Briefly, the diaphragm was located by placing the transducer in the intercostal space above the right 10th rib in the midaxillary or anteroaxillary line and directing the ultrasound beam perpendicular to the diaphragm (Fig. 1a). The zone of apposition was assessed at 0.5–2 cm below the costophrenic sinus. The inferior border of the costophrenic sinus was identified at end-inspiration as the zone of transition from the artefactual representation of normal lung (the lung sliding) to the visualization of diaphragm and liver. The diaphragm thickness was recorded in time motion (TM) mode. The sweep speed was adjusted as slow as possible to obtain a minimum of three cycles on the same image. The diaphragm was outlined by the two clear bright parallel lines of the pleural and peritoneal membranes (Fig. 1b and Online Videos). Several images were recorded and images were

Fig. 1 Probe placement to explore the diaphragm in the zone of apposition (**a**), with the ultrasonographic view of the normal diaphragm in the zone of apposition (**b**) and illustration of the measurement of diaphragm thickness at end-inspiration and end-expiration in TM mode (**c**). T_{EI} thickness at end-inspiration, T_{EE} thickness at end-expiration



TEI, thickness at end inspiration; TEE, thickness at end expiration.

deemed invalid if the two clear bright parallel lines of the pleural and peritoneal membranes were not plainly identified at each moment of the respiratory cycle. Ultrasonographic recordings were stored on compact disks, and a subsequent computer-assisted quantitative analysis was performed by a trained investigator who was unaware of the ventilatory condition. The measurements included diaphragm thickness at end-expiration (T_{EE}) and at end-inspiration (T_{EI}). When airway pressure could not be displayed on the screen of the Echo-Doppler machine to match the ultrasound tracings to the respiratory cycle (during SB), T_{EE} was measured just before the thickening start and T_{EI} was measured at maximal thickening. Measurements were averaged out of three or more consecutive breaths on the last valid image recorded at the end of each period. The thickening fraction (TF) was calculated as $(T_{EI} - T_{EE})/T_{EE}$ and expressed as a percentage (Fig. 1c).

Flow and pressure measurements

Flow was measured using a Fleisch N°2 pneumotachograph (Fleisch, Lausanne, Switzerland) connected to a differential (± 2 cmH₂O) pressure transducer (MP45, Validyne, Northridge, CA) and placed between the face mask and the ventilator Y connector. Airway opening pressure was measured between the ventilator circuit and the pneumotachograph using a pressure transducer (MP45, ± 100 cmH₂O). Oesophageal (P_{es}) and gastric pressures (P_{ga}) were measured using a double-balloon catheter (Marquat, Boissy Saint Léger, France) as previously described with appropriate placement checked and artefacts eliminated (see Supplementary Material for details) [20, 21]. Transdiaphragmatic pressure (P_{di}) was obtained by electronic subtraction of the P_{es} signal from the P_{ga} signal over at least ten consecutive breaths selected at the end of the pressure and flow recordings. The

transdiaphragmatic pressure–time product (PTP_{di}) per breath was obtained by measuring the area under the P_{di} signal from the onset of its positive deflection to its return to baseline. A difference between the beginning of the negative oesophageal-pressure deflection and the zero-flow point was taken as reflecting intrinsic PEEP [22] and was corrected for any abdominal pressure activity [23].

Assessment of TF reproducibility

Ten recordings (from ten separate patients) were randomly selected from the study to assess analyser reproducibility. The same sets of recordings were analysed twice by the same ultrasonographer to assess intra-analyser reproducibility and separately by two different ultrasonographers to assess inter-analyser reproducibility. Observer reproducibility was assessed in five additional patients (not included in the study) under NIV and during SB [24]. The two ultrasonographers performed separate recordings in these patients, one of them performing them twice in each patient (30 recordings in total). Multiple recordings on the same patient were performed in a blind fashion and separated by a time interval of 5–10 min. Each ultrasonographer subsequently analysed his recordings. Repeated measurements obtained in each patient from the same ultrasonographer were compared to assess intra-observer reproducibility. Inter-observer reproducibility was assessed by comparing measurements obtained separately from the two ultrasonographers in the same patient.

Statistical analysis

Data were analysed using the SPSS Base 13.0 statistical software package (SPSS, Inc, Chicago, IL). Continuous variables are reported as median (25–75th percentiles).

Friedman test and Wilcoxon paired tests (with post hoc Bonferroni correction) were used to assess differences between related variables. Correlations between TF and respiratory variables were assessed as well as those between the directional changes (absolute difference) in TF and in PTP_{di} . All correlations were calculated using the Spearman method and performed for the entire data set (including all four respiratory conditions of each patient) because of the limited sample size. The reproducibility is expressed by the intra-class correlation coefficient [25] and the coefficient of repeatability [26], as proposed by Bland and Altman. Intra-class correlation coefficient was determined with consistency and 95 % confidence interval. Coefficient of repeatability is calculated as the British Standards Institution repeatability coefficient (twice the standard deviation of the differences in repeated measurements) [26]. Two-tailed p values less than 0.05 were considered significant.

Results

Patients' characteristics

Fourteen patients were screened for the study. Of these, two could not be assessed because of poor ultrasonographic image quality. Twelve patients were therefore included in the comparison study. Their clinical characteristics are listed in Table 1.

Ultrasonography and pressure measurements

Respiratory data and ultrasound measurements are reported in Table 2. As expected, the tidal volume increased with increasing PS, but the respiratory rate did not significantly change. Increasing PS was associated

Table 1 Characteristics of patients

Patient	Age (years)	Male sex	SAPS II at ICU admission	APACHE score at inclusion	Days of MV	COPD	Reason for intubation	Measurement possible
1	77	No	38	9	6	No	Pneumonia and cardiogenic pulmonary edema	Yes
2	80	No	39	13	3	No	Cardiogenic pulmonary edema	Yes
3	79	Yes	37	15	1	No	Aspiration	Yes
4	71	No	45	15	8	No	Cardiac tamponade	Yes
5	75	No	39	8	2	No	Cardiogenic pulmonary edema	Yes
6	69	No	64	17	5	No	Endocarditis	Yes
7	24	Yes	34	16	42	No	Pneumonia	Yes
8	75	Yes	70	20	2	No	Cardiogenic pulmonary edema	Yes
9	72	Yes	56	12	6	No	Cardiogenic pulmonary edema	Yes
10	49	Yes	41	18	17	Yes	Septic shock	Yes
11	69	Yes	63	15	6	Yes	Status epilepticus	Yes
12	77	Yes	32	23	17	No	Pneumonia	Yes
13	83	Yes	62	16	2	No	Cardiogenic pulmonary edema	No
14	76	Yes	39	12	7	Yes	Cardiogenic pulmonary edema	No

MV mechanical ventilation, SAPS II simplified acute physiologic score II

Table 2 Respiratory and ultrasonographic data

	SB	PS 5	PS 10	PS 15
V_T , mL	–	324 (231–379)	402 (374–461) [#]	445 (388–547) [#]
RR, bpm	21 (18–28)	20 (18–28)	22 (19–30)	21 (17–29)
T_{EE} , mm	2.19 (1.94–2.76)	2.26 (1.78–2.46)	2.29 (1.84–2.52)	2.27 (2.06–2.88)
T_{EI} , mm	3.08 (2.77–4.77)	3.08 (2.34–3.51)	2.73 (2.39–3.25)	2.58 (2.34–3.56)
TF, %	47.5 (35.9–63.2)	36.2 (18.6–47.2) [*]	22.0 (9.6–28.2) ^{*,#}	16.3 (9.2–20.8) ^{*,#}
PTP_{di} , cmH ₂ O s	13.5 (8.1–16.9)	6.2 (4.7–8.0) [*]	4.0 (3.3–5.4) ^{*,#}	2.7 (2.1–4.3) ^{*,#}

V_T tidal volume, RR respiratory rate, PTP_{di} diaphragmatic pressure–time product, T_{EI} thickness at end-inspiration, T_{EE} thickness at end-expiration, TF thickening fraction, SB spontaneous breathing, PS 5 pressure support level of 5 cmH₂O, PS 10

pressure support level of 10 cmH₂O, PS 15 pressure support level of 15 cmH₂O

^{*} $p < 0.05$ as compared to SB; [#] $p < 0.05$ as compared to PS 5; [†] $p < 0.05$ as compared to PS 10

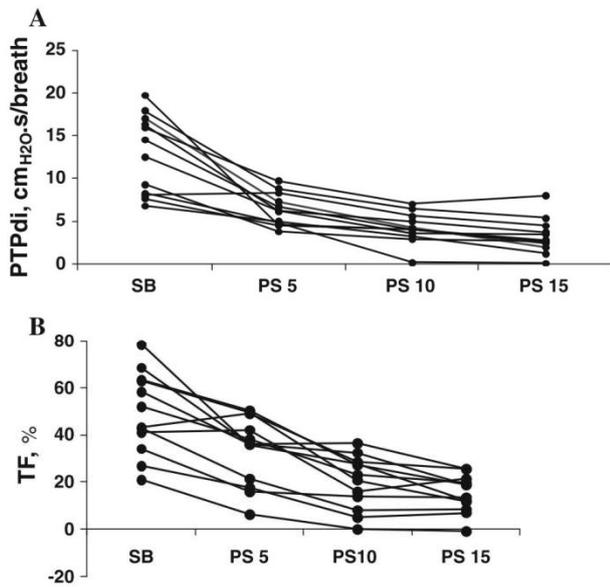


Fig. 2 Diaphragmatic pressure–time product (a) and thickening fraction (b) during spontaneous breathing and during non-invasive ventilation at different pressure support levels. PTP_{di} diaphragmatic pressure–time product, TF thickening fraction, SB spontaneous breathing, PS 5 pressure support level of 5 cmH₂O, PS 10 pressure support level of 10 cmH₂O, PS 15 pressure support level of 15 cmH₂O

with decreased PTP_{di} and TF (Table 2; Fig. 2). TF was significantly correlated with PTP_{di} ($\rho = 0.74$, $p < 0.001$; Fig. 3) but not with expired tidal volume ($\rho = -0.05$, $p = 0.76$). There was also a significant correlation between TF and PTP_{di} expressed per minute ($\rho = 0.52$, $p < 0.001$). The directional changes in TF after a change in the PS level followed reasonably with those in PTP_{di} , with a correlation coefficient of 0.35 ($p = 0.04$).

Reproducibility of TF

Repeatability measurements are reported in Table 3. Intra-class correlation coefficients were all above 0.97.

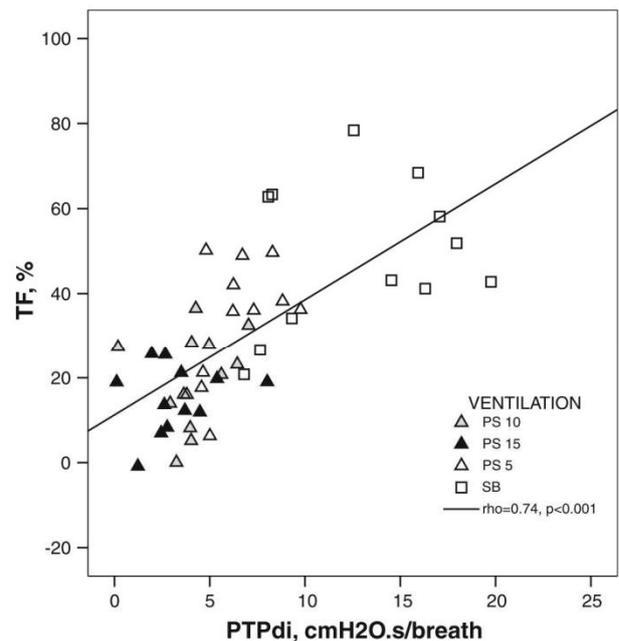


Fig. 3 Correlation between diaphragmatic pressure–time product and thickening fraction. PTP_{di} diaphragmatic pressure–time product, TF thickening fraction, SB spontaneous breathing, PS 5 pressure support level of 5 cmH₂O, PS 10 pressure support level of 10 cmH₂O, PS 15 pressure support level of 15 cmH₂O

Coefficients of repeatability ranged around 7–8 % for intra- or inter-analysers repeatability and around 15–18 % for intra- or inter-observer repeatability.

Discussion

This preliminary study is the first to evaluate the usefulness of diaphragm thickening to assess work of breathing in ICU patients. We found a parallel decrease in PTP_{di} and TF during NIV with increasing PS level and there was a good correlation between the two parameters.

Table 3 Thickening fraction reproducibility

	Intra-class correlation coefficient	Coefficient of repeatability, %
Intra-analyser reproducibility	0.987 [0.948–0.997]	7.3
Inter-analyser reproducibility	0.985 [0.939–0.996]	7.9
Intra-observer reproducibility	0.985 [0.943–0.996]	15.2
Inter-observer reproducibility	0.978 [0.916–0.995]	17.8

Diaphragmatic pressure–time product per breath (PTP_{di}), which is the integration of the area under the transdiaphragmatic pressure curve versus time, is a very useful tool for quantifying respiratory muscle effort in mechanically ventilated patients and assess the oxygen cost of breathing [27]. It is one of the most direct measures of patient effort, but its execution requires considerable attention, confining its use to the research setting [28–30]. We used this method as a reference standard to evaluate the accuracy of an alternative non-invasive method to assess diaphragmatic function and its contribution to respiratory workload. Ultrasonography can be used to directly image the diaphragm. Its identification depends upon bright echoes reflected from the attached parietal pleural and peritoneal membranes [31]. Ultrasonography has been previously used to monitor displacement of the diaphragm dome during respiratory manoeuvres with a 3–5 MHz transducer [14, 32–34]. It has also been used to assess the length and thickness of the zone of apposition against the rib cage, at different lung volumes in 2D mode [35] or TM mode [15, 36, 37]. Because the costal part of the diaphragm is relatively close to the skin surface, it is possible to use a 8–15 MHz transducer in this setting, which has less penetration but enhanced resolution.

Data from a necropsy study indicate that measurement of diaphragm thickness with ultrasonography in the zone of apposition is as accurate as measurements performed *in vitro* with a ruler [15]. These authors also showed that ultrasound measurement of diaphragm thickness changes during contraction (namely the TF), was possible using the TM mode and linearly correlated with lung volumes in spontaneously breathing healthy volunteers [15]. In our study, it was interesting to note that TF values did not correlate with expired volumes. In fact, using different levels of PS ventilation, the expired volume was determined not only by the respiratory effort, but also by the pressure provided by the ventilator. Our results therefore show that during NIV, thickening of the diaphragm reflects muscle effort and not the increase in pulmonary volume induced by ventilation. In fact, we found a parallel decrease in PTP_{di} and TF with increasing PS and a significant correlation between both parameters. Diaphragm thickening monitoring was recently proposed to assess for potential functional recovery from diaphragm

weakness or paralysis [38]. Our study suggests that the TF could be used in the ICU setting to assess diaphragmatic function and its contribution to respiratory workload in various situations, including ventilator-induced diaphragmatic dysfunction and ICU-acquired paresis. Moreover, because the directional changes in TF after a change in the PS level followed reasonably with those in PTP_{di} , TF seems promising in providing relevant information on patients' ventilatory support needs.

A common limitation of validation studies is reporting of reproducibility based solely on repeated analyses of the same recordings. We therefore assessed reproducibility based on repeated recordings in addition to repeated analyses [24]. Mathematically, the intra-class correlation coefficient is the proportion of the total variance which is due to the variation between the subjects [39]. An intra-class correlation coefficient of 1 indicates that the total variance is due solely to the variation between the subjects, there being no contribution to the total variance from variation between the observers; whereas an intra-class correlation coefficient of 0 indicates that none of the total variance is due to variation between subjects and all the total variance is attributed to variation between observers. We found an overall good repeatability of TF assessment, with intra-class correlation coefficients well above the 0.75 cut-off usually considered to indicate good agreement [40]. This finding is similar to a previous study reporting a good reproducibility of this index [15]. The coefficient of repeatability which is expressed in the measurement units is directly related to the 95 % limits of agreement and is the smallest significant difference between repeated measurements [26]. In our study, the coefficient of repeatability was high for intra-observer and inter-observer reproducibility (15–18 %). In clinical practice, an 18 % absolute change or difference in TF may therefore be required for accurate interpretation if the recordings are made and analysed by different observers or over prolonged intervals. Whether this agreement is acceptable or not depends on the range of the measurements encountered in clinical practice [26]. In our work, TF values ranged from 0 to 80 % for the clinical study. Median values of TF dropped by more than 30 % between SB and PS at the highest level of 15 cmH₂O. The relatively high coefficient of repeatability of inter-observer reproducibility highlights the fact that the repeatability of recordings may be difficult to achieve in some patients. In fact, the precise localisation of the zone of apposition and achievement of a stable ultrasound tracing are not simple, especially in case of increased respiratory workload. In addition the experience of the ultrasonographer is of importance, as with other echographic tools. On the other hand, the intrinsic respiratory variability of the patient may explain part of the variations observed when assessing the repeatability of the method because measurements were separated by a time interval of 5–10 min and only few cycles were selected for the measurements.

The rhythmic activity of the respiratory central pattern generators is characterized by a breath-to-breath variability, which differs from patient to patient and is influenced by the respiratory load [41]. Using only three respiratory cycles for TF measurement as previously suggested [15, 37] may be insufficient in patients with a high respiratory variability. Future studies may consider using a minimum of ten respiratory cycles to measure TF, as is the standard for PTP_{di} measurements. In addition, although all efforts were made to maintain the probe exactly on the same location during the entire study protocol, we can not exclude subtle displacements that may have altered the reproducibility.

Our study has some limitations. First, we only assessed the right hemi-diaphragm because its visualization is easier as compared to the left side whose imaging is often impeded by gastric and intestinal gas interposition. Second, we could not explore two patients because of poor quality images and this preliminary study has a limited sample size. Third, we studied a specific group of patients during post-extubation pressure NIV. Our results may

need replication in other patients groups. In particular, whether higher PEEP levels may influence the feasibility and accuracy of the methods needs to be assessed. In fact, lung volume changes may induce a displacement of the upper border of the zone of apposition [42]. In particular, the value of this technique needs to be assessed further in COPD patients, especially as different types of hyperaeration distribution in the lung parenchyma may affect diaphragm shape and motion [43].

In conclusion, we found a parallel decrease in TF and PTP_{di} during NIV with increasing levels of PS. The two parameters were significantly correlated. TF may prove useful in assessing diaphragmatic function and its contribution to respiratory workload in the ICU setting, but further studies are needed to assess this technique in a greater number of patients with various diseases.

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Electronic Supplementary Material

Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation

Emmanuel Vivier, Armand Mekontso Dessap, Saoussen Dimassi, Frederic Vargas, Aissam Lyazidi, Arnaud Thille, Laurent Brochard.

SUPPLEMENTAL METHODS

Flow and pressure measurements

Flow was measured using a Fleisch N°2 pneumotachograph (Fleisch, Lausanne, Switzerland) connected to a differential (± 2 cm H₂O) pressure transducer (MP45, Validyne, Northridge, CA) and placed between the facemask and the ventilator Y connector. Airway opening pressure was measured between the ventilator circuit and the pneumotachograph using a pressure transducer (MP45, ± 100 cm H₂O). Esophageal (Pes) and gastric pressures (Pga) were measured using a double-balloon catheter (Marquat, Boissy Saint Léger, France) inserted through the nose after topical anesthesia and advanced until the distal balloon was in the stomach and the proximal balloon was in the middle portion of the esophagus. Each balloon was filled with 1 mL of air and connected to a pressure transducer (MP45, ± 100 cm H₂O). Appropriate placement of the esophageal balloon was assessed by performing an occlusion test [1, 2]. Gastric balloon position was evaluated by checking whether gentle manual pressure on the abdomen generated Pga fluctuations and that the sharp Pes increase caused by esophageal contraction during swallowing was absent in the Pga trace [1, 2]. Transdiaphragmatic pressure (Pdi) was obtained by electronic subtraction of the Pes signal from the Pga signal. Pressure and flow signals were digitized on a personal computer at 200 Hz and sampled using an analog-to-digital converter system (MP100;

Biopac Systems, Santa Barbara, CA). After elimination of artifacts produced by coughing and esophageal spasms, mean values were computed over at least 10 consecutive breaths and used for the analysis. The transdiaphragmatic pressure-time product (PTP_{di}) per breath was obtained by measuring the area under the P_{di} signal from the onset of its positive deflection to its return to baseline. A difference between the beginning of the negative esophageal-pressure deflection and the zero-flow point was taken as reflecting intrinsic PEEP [3] and was corrected for any abdominal pressure activity [4].

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Travail n°1

Determinants of diaphragm thickening fraction during mechanical ventilation: an ancillary study of a randomized trial

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Determinants of diaphragm thickening fraction during mechanical ventilation: an ancillary study of a randomised trial

To the Editor:

Ultrasonography of the diaphragm is the subject of a growing interest in the intensive care unit (ICU) setting [1–6]. Observing the diaphragm in its zone of apposition allows measurement of its thickness and computation of its thickening fraction (TFdi), which depends on diaphragmatic activity [3] and reflects the diaphragm work of breathing [1]. A recent study showed that the TFdi correlated well with the endotracheal pressure variation generated by phrenic stimulation [6]. This index was also proposed for clinical evaluation of diaphragm weakness to detect ventilator-induced diaphragmatic dysfunction (VIDD) and predict difficult weaning [3, 4]. However, it remains unclear whether increased thickening in this setting only reflects a better intrinsic diaphragmatic strength, or if it also suggests enhanced work of breathing in response to increased cardiorespiratory workload. Furthermore, some authors suggested that VIDD could be thought as the “respiratory” manifestation of a global neuromuscular weakness [4, 7], but its relationship with ICU-acquired limb weakness is not straightforward [5]. The present study had a dual objective: first, to explore the correlation between ICU-acquired limb weakness (as assessed by the Medical Research Council (MRC) score) and diaphragm thickening (as assessed by TFdi); second, to assess the association of clinical variables with TFdi during mechanical ventilation.

This was a planned *a priori* ancillary study performed in one (Henri Mondor University Hospital, Creteil, France) of the nine participating centres of the B-type natriuretic peptide for the fluid Management of Weaning (BMW) trial [8]. We explored diaphragm thickening at the very beginning of weaning in 55 consecutive participants enrolled in this trial at this centre when ultrasonography was available. Ultrasonography was performed after 5 min of minimal respiratory support (pressure support set at 7 cmH₂O with zero end expiratory pressure), using an Envisor system (Philips Ultrasound, Bothell, WA, USA) equipped with a 12 MHz high-resolution ultrasound linear probe. After locating the right hemi-diaphragm zone of apposition, the end-inspiratory and end-expiratory thicknesses were measured, allowing calculation of the TFdi of each patient, as previously reported [1]. The ultrasonography scans were performed by two intensivists, both experienced in ultrasonography (E. Vivier or F. Roche-Campo) and all measurements were analysed by E. Vivier. ICU-acquired weakness was screened in cooperating patients by clinical assessment of the limb strength, using the MRC score [9]. The most clinically relevant variables concerning diaphragmatic strength were used for the statistical analysis.

Spearman coefficients were computed to test pairwise correlations. These correlations were further used to build a focused principal component analysis (FPCA; “psy” package, R 3.2.2, the R Foundation for Statistical Computing, Vienna, Austria), using TFdi as the dependent variable and allowing a simple graphical display of correlation structures of clinical variables recorded before diaphragm ultrasonography [8].

We found no correlation between TFdi and MRC score (Spearman’s rho correlation coefficient -0.07 ; $p=0.62$) (figure 1a). FPCA using TFdi as outcome variable and variables collected prior to inclusion as independent variables revealed two main clusters and one isolated covariate (figure 1b): the first cluster included variables significantly positively correlated with TFdi: older age, cardiac and respiratory comorbidities (including chronic cor pulmonale, chronic obstructive pulmonary disease) and higher values of arterial carbon dioxide tension (P_{aCO_2}) at inclusion; the second cluster included ICU treatments (need for neuromuscular blockade or vasopressor) and complications (ventilator-associated pneumonia and



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Diaphragm thickening does not correlate with ICUAW; it is influenced by cardiopulmonary load and residual sedation <http://ow.ly/6TC130e6G3Q>

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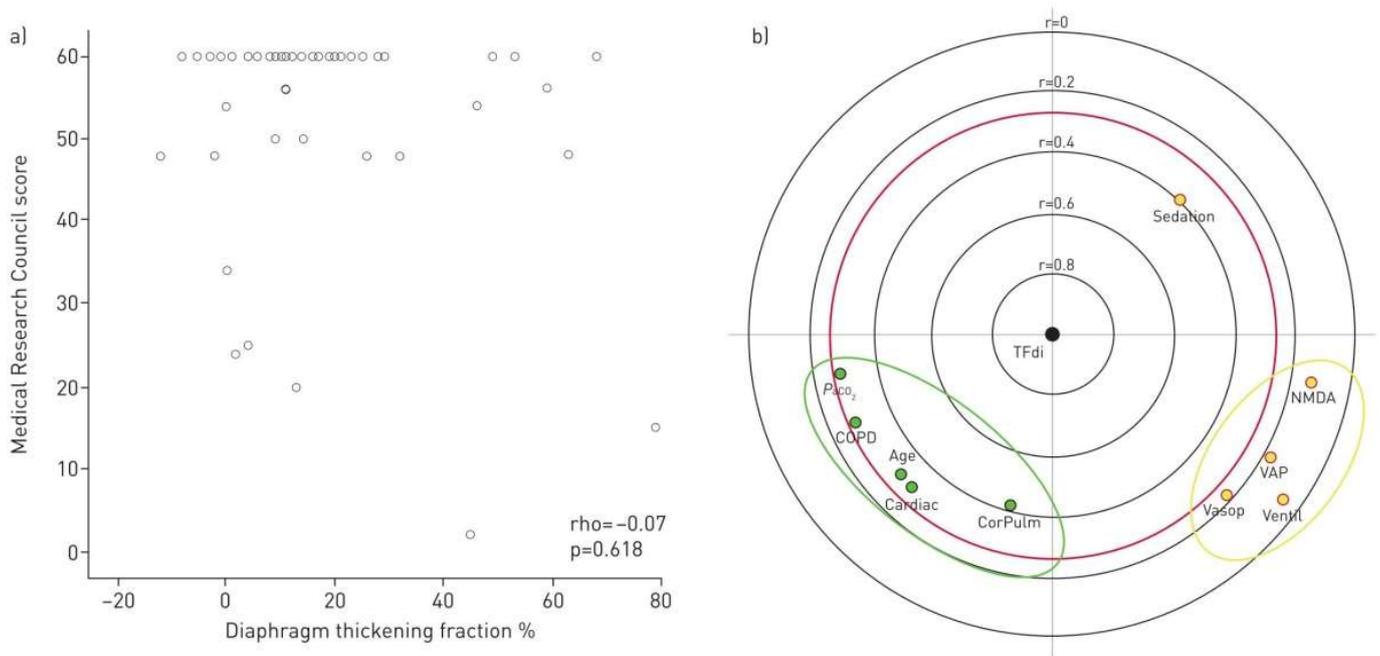


FIGURE 1 Correlation between Medical Research Council score and diaphragm thickening fraction in ventilated patients at initiation of weaning (a), and focused principal component analysis (FPCA) of diaphragmatic thickening fraction and patient characteristics (b). FPCA is a simple graphical display of correlation structures focusing on a particular dependent variable. The display reflects primarily the correlations between the dependent variable and all other variables (covariates) and secondarily the correlations among the covariates. The dependent variable (thickening fraction) is at the centre of the diagram and the distance of this point to a covariate faithfully represents their pairwise Spearman correlation coefficient (using ranked values of continuous variables). Covariates are positively correlated to the dependent variable, whereas yellow covariates are negatively correlated to the dependent variable. Covariates displayed inside the red circle are significantly correlated to the dependent variable ($p < 0.05$). The diagram also shows relationships between covariates as follows: correlated covariates are close (for positive correlations, allowing identification of clusters, as shown within the green or yellow ellipses) or diametrically opposite vis-à-vis the origin (for negative correlations) whereas independent covariates make a right angle with the origin. TFdi: diaphragmatic thickening fraction; Cardiac: any chronic cardiac disease; COPD: chronic obstructive pulmonary disease; CorPulm: chronic cor pulmonale; Age: age at inclusion; P_{aCO_2} : arterial carbon dioxide tension at inclusion; Sedation: days not free from sedation before inclusion; NMDA: use of neuromuscular blockers before inclusion; VAP: ventilator-associated pneumonia before inclusion; Vasop: vasopressor use before inclusion; Ventil: days with ventilation before inclusion.

duration of ventilation) which had a negative but non-significant correlation with TFdi; last, the sedation burden (as assessed by the number of days not free from sedation) was significantly negatively correlated with TF.

It has been suggested that diaphragmatic dysfunction in patients receiving mechanical ventilation may be part of a global ICU-acquired weakness (ICU-AW) [7]. However, recent data seem to contradict this hypothesis [4, 5]. While DRES *et al.* [5] found a very weak correlation ($\rho = 0.28$, $p = 0.01$) between MRC score and TFdi, we did not find any significant association between these variables. Although these two clinical assessment methods are different in nature (one is volitional and the other is objective), these results provide an argument in favour of an alternative impairment of the diaphragm.

The TFdi measured in the zone of apposition is inversely related to its shortening as the muscle volume remains constant [10]. This index reflects the work of breathing developed by the diaphragm in response to a given load; it can reflect intrinsic diaphragm strength (allowing diagnosis of diaphragm paresis or paralysis) but it is also influenced by the magnitude of the load imposed to the respiratory system, as shown during noninvasive or invasive assisted ventilation [1, 11]. In our series, patients with a higher TFdi at initiation of weaning suffered more often from chronic cardiac or pulmonary disease and had a higher P_{aCO_2} at weaning initiation than their counterparts. The thickening fraction was recorded with the same ventilator settings (minimal pressure support level) in all patients. A higher TFdi may be the expression of augmented work of breathing in response to an increased cardiorespiratory load imposed on the diaphragmatic muscle when assessed under spontaneous breathing conditions [1, 11]. The thickening of the diaphragm in its zone of apposition may potentiate the diaphragmatic excursion when facing an increase in physiological (maximum inspiration) or pathological (dyspnoea) load in a well-awake patient. The significant negative correlation of TFdi with sedation suggests an influence of prolonged or residual sedation on respiratory drive and/or diaphragm function. Sedation exerts a well-known inhibitory effect on diaphragmatic contractility [12, 13]. Diaphragmatic activity may be jeopardised by a residual sedation,

especially in the early weaning period [14]. Last, TFdi was negatively but not significantly associated with early ICU treatments (neuromuscular blockers or vasopressor use before inclusion) and complications (ventilator-associated pneumonia and prolonged ventilation), which may be risk factors for diaphragmatic atrophy and weakness [15]. The lack of significance of these associations may be due at least in part to the small size of our cohort.

The strengths of our study include the standardisation of ventilator setting during diaphragm ultrasonography and the early assessment of TFdi at the initiation of weaning. However, two limitations must be considered: first, we did not compare the diaphragm thickening fraction to a clinical indicator of inspiratory force (such as maximal inspiratory pressure at the airways); second, the low interobserver reproducibility of TFdi values [1, 3] requires caution when interpreting our data in the clinical scenario.

In conclusion, our data corroborate recent studies reporting no tight association between diaphragm activity and limb weakness in critically ill patients. We observed a positive correlation between cardiopulmonary comorbidities and TFdi suggesting a possible influence of respiratory load on TFdi when assessed under minimal respiratory support. Conversely, a negative correlation between exposure to sedation and TFdi suggested an impairment of diaphragm activity by residual sedation.

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Travail n°2

Atrophy of Diaphragm and Pectoral Muscles in Critically Ill Patients.

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ANESTHESIOLOGY

Atrophy of Diaphragm and Pectoral Muscles in Critically Ill Patients

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Critical illnesses often lead to early muscle wasting.^{1,2} The muscular atrophy that affects respiratory and peripheral muscles can be explained by many physiologic mechanisms including mitochondrial dysfunction, protein catabolism, microvascular alterations, inactivation of sodium channels, alteration in calcium homeostasis, and tensile integrity impairment.³ A more specific involvement of diaphragm fibers may directly be caused by the aggressive action of both sepsis and the mechanical ventilation support,^{4–7} leading to ventilator-induced diaphragm dysfunction.⁸ The subsequent impairment of diaphragm contractility and the reduction of its muscle mass are associated with prolonged weaning and poor outcome.^{8,9} Under normal conditions, the muscle fibers of the diaphragm contract a dozen of times per minute; however, in artificial inactivation of the diaphragm, by sedation or paralysis, such contractions are suddenly arrested, incurring muscular atrophy which could happen earlier than that of peripheral muscles (especially nonpostural muscles with mainly phasic function, which usually contract on demand and have a low inactive tonus).⁴

Several studies^{10–12} have demonstrated that ultrasonography is a good tool to visualize and measure the apposition zone of the diaphragm with a good accuracy. We designed the present work to assess diaphragm muscle atrophy during the first days of critical illness, and to describe its determinants. The main objective of the study was to detect a clinically significant decrease in diaphragm thickness assessed by ultrasonography at day 5. To scrutinize the possible role of diaphragm inactivity in the occurrence of its muscle

ABSTRACT

Background: Muscle atrophy occurs early during critical illnesses. Although diffuse, this atrophy may specifically affect the diaphragm under artificial inactivity accompanying invasive mechanical ventilation. The primary objective of this study was to highlight diaphragm atrophy during the first 5 days of critical illness. Monitoring of pectoral thickness (a nonpostural muscle with mainly phasic function) served as a control.

Methods: Diaphragm and pectoral thicknesses were measured by ultrasound within the first 24 h of admission in 97 critically ill patients, including 62 on mechanical ventilation. Thirty-five patients were reexamined at day 5.

Results: Baseline median (interquartile) values of diaphragm and pectoral thicknesses at day 1 were 2.4 (2.0, 2.9) and 5.9 (4.7, 7.2) mm, respectively ($n = 97$). Higher values of diaphragm thickness at baseline were positively associated with male sex, chronic obstructive pulmonary disease, and diabetes. Diaphragm and pectoral atrophies (defined as a decrease of 10% or more between day 1 and day 5) were detected in 48% (17 of 35) and 29% (10 of 34) respectively, and were uncorrelated with each other. Diaphragm atrophy was significantly more frequent in patients with septic shock and in those with mechanical ventilation, as compared with their respective counterparts (71% [10 of 14] vs. 33% [7 of 21], $P = 0.027$ and 71% [17 of 28] vs. 0% [0 of 7], $P = 0.004$, respectively), whereas pectoral atrophy was more common in patients treated with steroids as compared with their counterparts (58% [7 of 12] vs. 14% [3 of 22], $P = 0.006$). A statistically significant association between diaphragm atrophy and outcome was not found. Pectoral atrophy seemed associated with less successful weaning from mechanical ventilation at day 14 (12% [1 of 8] vs. 58% [11 of 19], $P = 0.043$).

Conclusions: Ultrasound enables identification of specific early diaphragm atrophy that affects the majority of mechanically ventilated patients and septic shock patients. Diaphragm atrophy and pectoral muscle atrophy seem to be two unrelated processes.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Muscle atrophy is common in the critically ill, and diaphragm atrophy occurs during mechanical ventilation. It is not known whether wasting of diaphragm and nondiaphragm muscle is related.

What This Article Tells Us That Is New

- Ultrasound was used for serial assessment of diaphragm and pectoral muscle in 97 critically ill patients. Diaphragm and pectoral atrophy occurred in 48% and 29%, respectively, and was associated with septic shock (diaphragm) and steroid use (pectoral); atrophy of the two muscle types appears unrelated.

This article is accompanied by an editorial on p. 462. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). For a downloadable PPT slide containing this article's citation information, please visit https://anesthesiology.pubs.asahq.org/ss/downloadable_slide.aspx. A.M.D. and G.C. contributed equally to this article.

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atrophy, we categorized patients by their need for mechanical ventilation. We also monitored the pectoral muscle, which is a nonpostural muscle, not involved in ventilation, and whose mechanism of atrophy could be independent of active breathing cessation.⁴ We hypothesized that diaphragm atrophy would be more pronounced than pectoral atrophy after forced, artificial inactivation of the former.

Materials and Methods

This observational, prospective, and monocentric study was approved by the French research ethic board Committee for the Protection of Persons Sud-Est II, Edouard Herriot Hospital, Lyon, France. It was conducted between June 2013 and January 2016 in a single intensive care unit (ICU). All included patients (or their relatives) provided written informed consent.

Study Population and Design

All patients consecutively admitted to the ICU were screened and enrolled in the study if they satisfied the following criteria in total: older than 18 yr of age, covered by the French social security system, nonopposition of the patient or relatives to participation in the trial. Patients were excluded if they had one of the following criteria: tracheostomy, chronic noninvasive or invasive ventilation, known diaphragmatic paralysis or neurologic disease with motor dysfunction, pregnancy, breast-feeding, ventilation longer than 24 h before hospitalization, an expected duration of ICU stay or mechanical ventilation (in ventilated patients) of less than five days, or a do-not-resuscitate order. Screening was only carried out when at least one of the ultrasound operators was present in the ICU. Inclusion

in the study did not interfere with the daily clinical management, especially weaning from mechanical ventilation, which was protocolled.¹³

Ultrasonography Measurements and Reproducibility

Ultrasound images of the right hemidiaphragm zone of apposition and of the right pectoral muscle were recorded for each patient on day 1, and repeated on day 5, when applicable. Follow-up on day 5 was not performed if one of the following events occurred: change of ventilation condition (*i.e.*, intubation or extubation), discharge from ICU, or death. Measurement sites (*i.e.*, diaphragm apposition on axillary line, and pectoral muscle) were marked with a transparent film to repeat the images exactly from the same points. Images were taken with Vivid S6 (General Electric Healthcare, USA) ultrasound machine with a 10-MHz probe. Right diaphragm thickness was measured with the technique described by Wait and Cohn on patients in semi-sitting position.^{11,14} The probe was placed on the right anterior axillary line. The diaphragm was identified as the hypoechoic zone sandwiched between the two hyperechoic lines: pleural and peritoneal membranes (fig. 1). Diaphragm thickness was measured on time movement and captured as the distance between the two lines at the end of expiration. The right pectoral muscle was observed under the clavicle, with the probe pointing to the coracoid process as described by Grechenig *et al.*¹⁵ (fig. 2). Images were taken by two trained operators (A.R. and E.V., certified for critical care ultrasonography) and analyzed offline by only one (E.V.); three measurements were averaged out for each patient on day 1, and day 5 when applicable. Muscle atrophy was quantified for each patient by dividing the change in thickness (thickness on day 5 minus thickness on day 1)

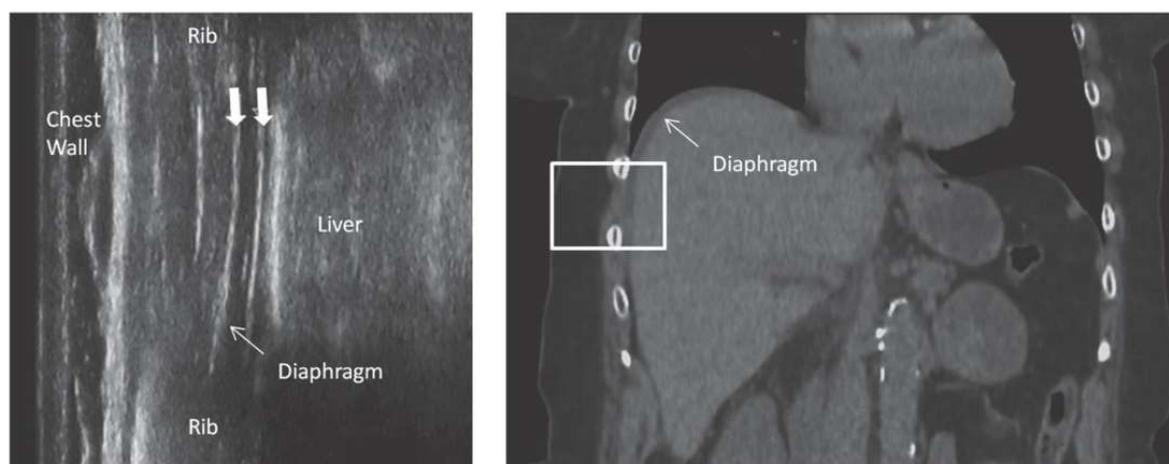


Fig. 1. Example of ultrasound visualization of the diaphragm at the zone of apposition (left panel) and comparative computed tomography scan (right panel). The diaphragm could be identified as the hypoechoic zone bounded by the two hyperechoic pleural and peritoneal layers (parallel arrows in the left panel).

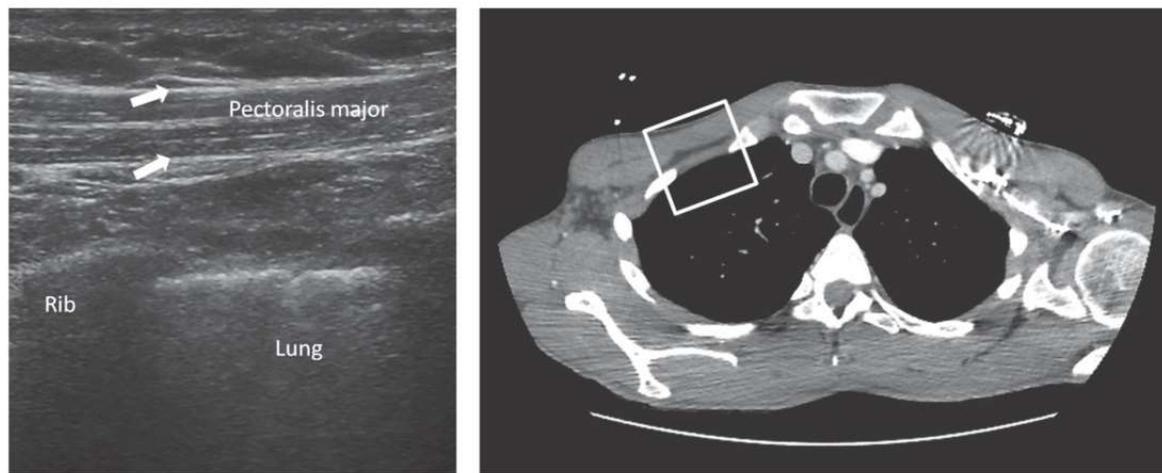


Fig. 2. Ultrasound image of the pectoral muscle under the clavicle (left panel), and comparative computed tomography scan (right panel). The pectoralis major is outlined by its two fasciae (arrows) and stands out in front of the pectoralis minor (visible on the left).

by the thickness on day 1 and expressing it as a percentage. Diaphragm atrophy was defined as a 10% or more relative decrease in diaphragm thickness between day 1 and day 5.¹⁶ The same definition could be applied for pectoral atrophy.

Agreement between the two observers was assessed in 20 patients from the study. The two ultrasonographers performed separate recordings of diaphragm and pectoral thicknesses for each patient, and these measurements were all analyzed and compared by one of them (E.V.).

Endpoints and Data Recording

The primary outcome was the change in diaphragm thickness between day 1 and day 5. The secondary endpoints were (1) percentage of pectoral atrophy on day 5, (2) clinical characteristics associated with baseline diaphragm and pectoral thickness, and (3) ICU characteristics and outcomes associated with diaphragm and pectoral atrophy. The following data were assessed at ICU admission: age (considering those of older than 65 yr as elderly patients at risk for sarcopenia),¹⁷ sex, weight, smoking history, comorbidities (including high blood pressure, cardiovascular disease, diabetes, and chronic obstructive pulmonary disease), admission diagnosis, and disease severity (assessed by Sequential Organ Failure Assessment and Simplified Acute Physiology Score II scores, where patient's condition is classified very severe with values greater than 7 and greater than 59, respectively).^{18,19} Some relevant ICU clinical characteristics were collected between day 1 and day 5, such as mechanical ventilation, septic shock (assessed by using Sepsis 3 definition),²⁰ muscle paralysis, use of sedation, and corticosteroid therapy (including low doses to treat septic shock). Successful weaning from mechanical ventilation at day 14 was defined as patient survival with definitive liberation

from invasive mechanical ventilation 14 days after inclusion in the study. In-ICU and in-hospital length of stay and mortality were also recorded.

Statistical Analysis

Based on a preliminary study showing a daily diaphragm thinning of 6% during mechanical ventilation,²¹ we hypothetically calculated an overall thinning of 20% from day 1 to day 5. With an estimated diaphragm thickness of 29 ± 3 mm at day 1,²² an α -risk (type I error) of 5%, and a statistical power of 90%, 33 patients requiring mechanical ventilation were deemed necessary to show a 20% reduction in diaphragm thickness between day 1 and day 5. Anticipating that 20% of included patients requiring mechanical ventilation would die or would be extubated before day 5, 40 patients with mechanical ventilation were considered necessary. However, we decided to include a minimum of 80 patients, of whom at least 40 were on mechanical ventilation, and 40 with spontaneous breathing.

Data were analyzed using IBM SPSS Statistics for Windows (Version 19.0, IBM Corp, USA). Results were reported as medians (first, third quartiles) or numbers (percentage). Mann-Whitney *U* test was used to compare continuous variables. Chi-square test or Fisher exact test were used to compare categorical variables, as appropriate. Diaphragm and pectoral muscle thickness changes from day 1 to day 5 were compared by Wilcoxon paired test. Spearman rank correlation coefficient was used for bivariate correlations. Two-sided *P* values less than 0.05 were considered significant. No outliers were detected during the analysis, and the data presented here are exhaustive.

The reproducibility was expressed by the intraclass correlation coefficient²³ and the coefficient of repeatability,²⁴

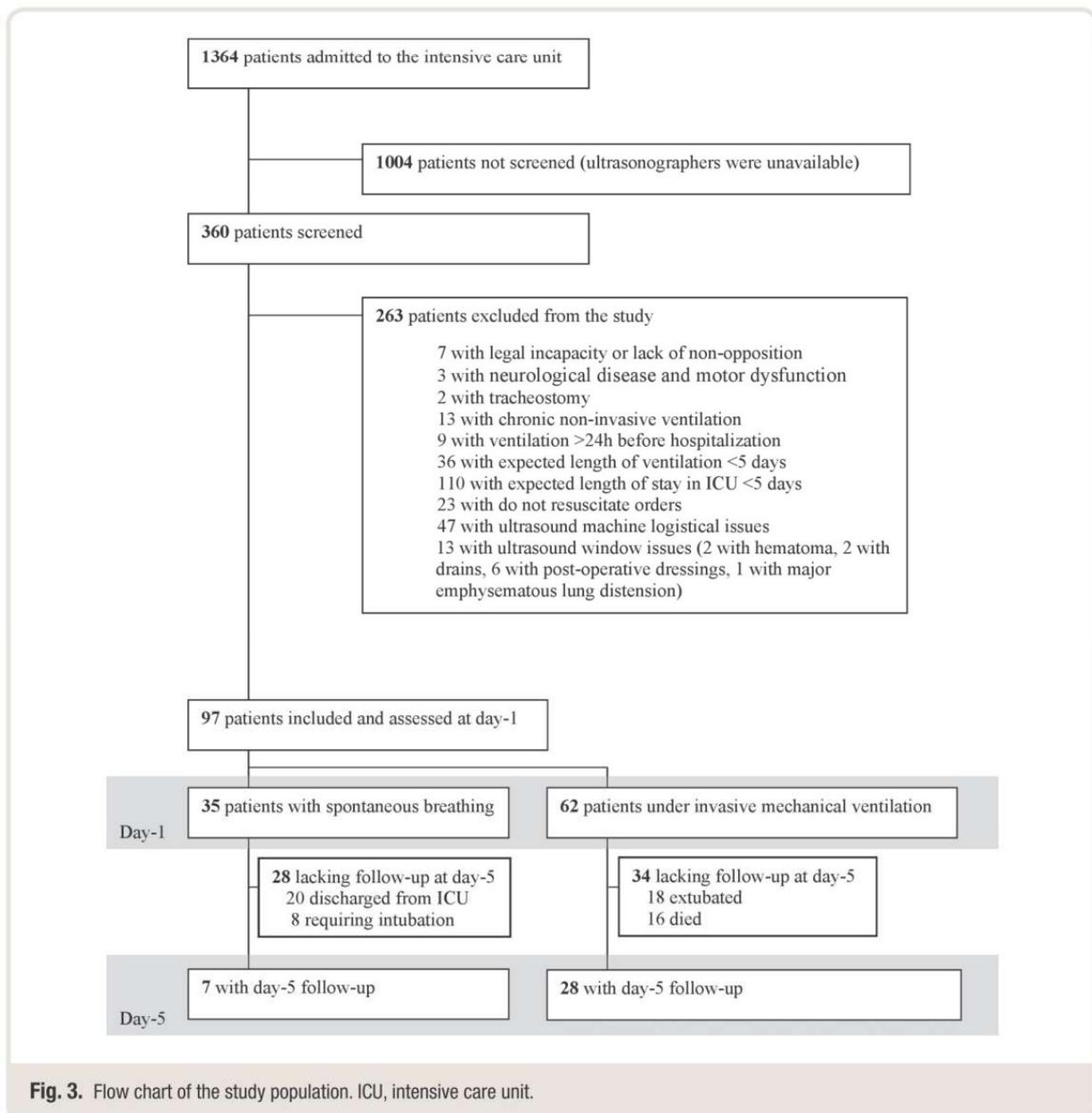
as proposed by Bland and Altman. Intraclass correlation coefficient was determined with consistency and 95% CI. Coefficient of repeatability was calculated using the British Standards Institution repeatability coefficient (twice the SD of the differences in repeated measurements).²⁴ The coefficient of repeatability is directly related to the 95% limits of agreement. It is expressed in the measurement units and is the smallest significant difference between repeated measurements.

Results

We herein report the primary and preplanned analysis of these data.

Patient Population and Follow-up

Ninety-seven patients were included in the study (fig. 3). At the time of inclusion, 62 patients were on mechanical ventilation and 35 were breathing spontaneously. Patient's clinical characteristics at ICU admission (day 1 cases [n = 97]) are listed in Supplemental Digital Content 1 (<http://links.lww.com/ALN/B929>). Among the 62 patients requiring mechanical ventilation, only 28 could be followed up on day 5; the remaining patients were either extubated (n = 18) or dead (n = 16) before day 5. Of the 35 spontaneously breathing patients, only seven could be followed up on day 5; the remainders were either intubated (n = 8)



or discharged from ICU ($n = 20$) between day 1 and day 5. Characteristics of patients followed up on day 5 (complete cases on day 5 [$n = 35$]) are reported in Supplemental Digital Content 2 (<http://links.lww.com/ALN/B930>).

Diaphragm and Pectoral Thicknesses

Diaphragm thickness was successfully assessed using ultrasound in all patients on day 1 and alike for pectoral thickness, except in one patient. At day 1, the whole population (day 1 cases [$n = 97$]) had a diaphragm and pectoral median thicknesses of 2.4 (2.0, 2.9) and 5.9 (4.7, 7.2) mm, respectively. At day 1, a higher diaphragm thickness was positively associated with male sex, diabetes, and chronic obstructive pulmonary disease, whereas the pectoral muscle was thicker in overweight (Supplemental Digital Content 3, <http://links.lww.com/ALN/B972>) and younger patients (table 1). The correlation between diaphragm and pectoral thicknesses at day 1 was not statistically significant ($\rho = 0.171$, $P = 0.095$; fig. 4). There was no significant association between baseline thicknesses and outcome (data not shown).

Diaphragm and Pectoral Atrophy

The marks on the chest wall were still present in all patients at day 5, on which the measurements of diaphragm and pectoral thicknesses could be repeated. In the overall population (complete cases on day 5 [$n = 35$]), a substantial thinning of the diaphragm was observed between day 1 and day 5 (from 2.5 [2.1, 3.0] to 2.1 [1.9, 2.5] mm, with a mean difference of 0.3 mm [95% CI, 0.2–0.5], $P < 0.001$, fig. 5A), whereas the change in pectoral thickness was not significant (from 5.6 [4.8, 6.9] to 5.9 [4.9, 7.0] mm, with a mean difference of 0.1 mm [95% CI, –0.3 to +0.5], $P = 0.308$, fig. 5B). The occurrence of diaphragm

and pectoral atrophies (as defined by a 10% or more relative decrease in thickness) were 48% (17 of 35) and 29% (10 of 34), respectively. There was no statistically significant correlation between the change in thickness of diaphragm and pectoral ($\rho = -0.02$, $P = 0.912$; fig. 4B). In *post hoc* subgroup analyses, pectoral atrophy occurred more in patients treated with steroids, whereas diaphragm atrophy occurred more in patients with mechanical ventilation, septic shock (Supplemental Digital Content 4, <http://links.lww.com/ALN/B973>), or multiple organ failure, as compared with their respective counterparts; other variables did not consistently influence diaphragm or pectoral atrophy (tables 2 and 3). *Post hoc* outcome analyses found that diaphragm atrophy was not associated with patient's outcomes, whereas pectoral atrophy was associated with less successful weaning at day 14 (Supplemental Digital Content 5, <http://links.lww.com/ALN/B931>).

Reproducibility

Intraclass correlation coefficient were 0.982 (95% CI, 0.955 to 0.993) and 0.985 (95% CI, 0.963 to 0.994) for diaphragm and pectoral thicknesses, respectively. Coefficients of repeatability were 0.3 and 0.9 mm for diaphragm and pectoral thicknesses, respectively.

Discussion

Baseline diaphragm and pectoral thicknesses were not homogeneous in the studied population and seemed influenced by different preexisting comorbidities but with no definite conclusion given the limited sample size. In the 35 patients followed from day 1 to day 5, we observed atrophy of diaphragm over the first days of the critical illness, especially in patients with mechanical ventilation, septic shock, or organ

Table 1. Diaphragm and Pectoral Thickness According to Patient Baseline Characteristics ($n = 97$)

		Diaphragm Thickness (mm)		Pectoral Thickness (mm)	
Sex	Male ($n = 68$)	2.6 (2.1–3.0)	$P = 0.042$	5.9 (4.7–7.2)	$P = 0.725$
	Female	2.1 (1.8–2.7)		5.5 (4.6–7.2)	
Elderly (Age older than 65 yr)	Yes ($n = 63$)	2.4 (2.0–3.0)	$P = 0.934$	5.6 (4.6–6.5)	$P = 0.016$
	No	2.3 (2.1–2.9)		6.9 (5.4–8.1)	
Overweight (BMI greater than 25 kg/m ²)	Yes ($n = 44$)	2.5 (2.1–3.0)	$P = 0.277$	6.4 (5.4–7.8)	$P = 0.004$
	No	2.3 (2.0–2.9)		5.4 (4.5–6.6)	
Hypertension	Yes ($n = 37$)	2.6 (2.1–3.0)	$P = 0.078$	6.1 (5.0–7.3)	$P = 0.215$
	No	2.2 (1.9–2.8)		5.5 (4.6–7.1)	
Diabetes	Yes ($n = 28$)	2.8 (2.1–3.2)	$P = 0.018$	6.5 (4.8–8.1)	$P = 0.242$
	No	2.3 (1.9–2.8)		5.8 (4.6–7.0)	
Smoking	Yes ($n = 36$)	2.6 (2.0–3.2)	$P = 0.394$	5.8 (4.6–7.9)	$P = 0.897$
	No	2.3 (2.0–2.9)		6.0 (4.7–7.0)	
COPD	Yes ($n = 29$)	2.8 (2.0–3.3)	$P = 0.019$	5.9 (4.8–7.7)	$P = 0.753$
	No	2.2 (2.0–3.0)		5.9 (4.6–7.1)	
Heart disease	Yes ($n = 41$)	2.3 (2.0–2.8)	$P = 0.589$	5.8 (4.7–6.9)	$P = 0.870$
	No	2.4 (2.0–3.1)		6.0 (4.6–7.6)	
Ventilation	MVS ($n = 62$)	2.3 (2.0–2.9)	$P = 0.340$	5.8 (4.7–7.3)	$P = 0.961$
	SB	2.7 (2.0–3.0)		6.0 (4.6–7.1)	

Data are median (interquartile range). BMI, body mass index; COPD, chronic obstructive pulmonary disease; MVS, Mechanical ventilation support; SB, spontaneous breathing.

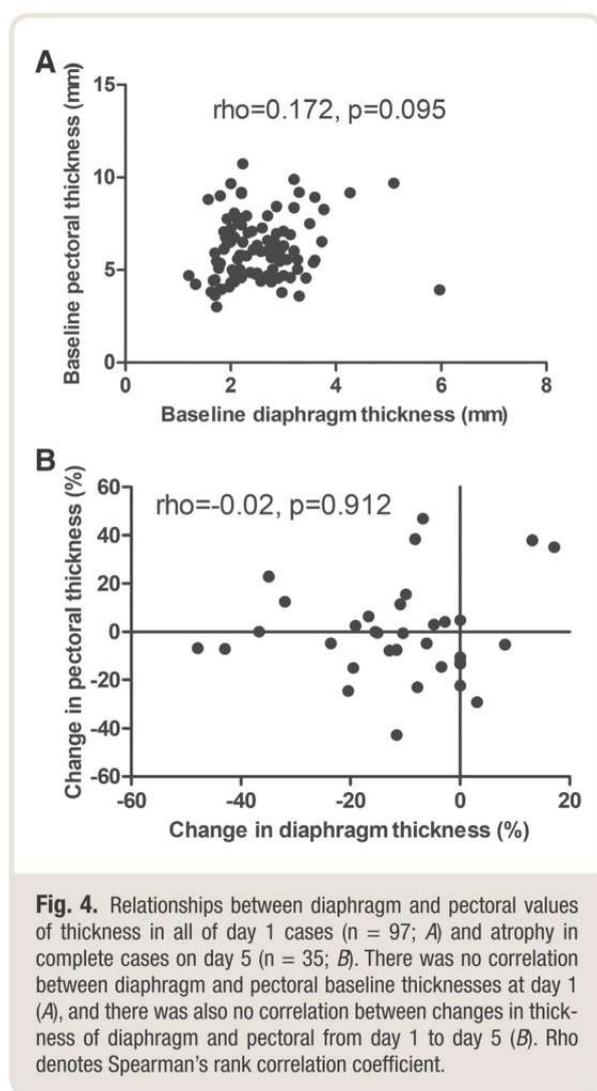


Fig. 4. Relationships between diaphragm and pectoral values of thickness in all of day 1 cases ($n = 97$; *A*) and atrophy in complete cases on day 5 ($n = 35$; *B*). There was no correlation between diaphragm and pectoral baseline thicknesses at day 1 (*A*), and there was also no correlation between changes in thickness of diaphragm and pectoral from day 1 to day 5 (*B*). ρ denotes Spearman's rank correlation coefficient.

failure. Pectoral atrophy happened more in patients treated with steroids during the first 5 days in ICU, and seemed associated with poor outcomes, unlike diaphragm atrophy.

Diaphragm and Pectoral Thicknesses

In this series of 97 patients, the diaphragm was thicker in men than in women, confirming previously reported data.²⁵ We also found a higher baseline diaphragm thickness in patients with chronic obstructive pulmonary disease, which is consistent with previous autopsy data demonstrating an increase of the number and size of diaphragm muscle fibers in emphysematous patients.^{26,27} Such muscular hypertrophy has been ascribed to excessive respiratory workload and lower muscular efficiency in chronic obstructive pulmonary disease patients.²⁸ This observation is also congruent with the greater diaphragm thickening recently reported in chronic obstructive pulmonary disease patients.²⁹ More surprisingly, diabetic

patients also had a thicker diaphragm than their counterparts. Several epidemiologic studies have shown a slight decrease in forced expiratory volume in diabetic patients, suggesting that diaphragm hypertrophy could have been induced by a workload-driven mechanism similar to that occurring in chronic obstructive pulmonary disease.^{30,31} On the other hand, other physiologic studies have suggested a decreased respiratory muscle strength in diabetics which could be the underlying mechanism.^{32,33} Further studies are essential to scrutinize the effect of diabetes on diaphragm thickness. The two factors associated with pectoral thickness in our series were age and obesity. Age classically generates sarcopenia,³⁴ whereas for obesity its role in precipitating peripheral trophicity remains controversial (although some studies reported an increase in lean muscles in obese individuals^{35,36}).

Diaphragm Atrophy

Our work corroborates the previous studies findings concerning the use of ultrasound to quantify early diaphragm atrophy in critically ill patients.^{16,21,25,37,38} On the contrary, pectoral atrophy was infrequent in our population. This discrepancy is congruent with the results of Levine *et al.*,⁴ who found a marked histologic atrophy of the diaphragm but not the pectoral muscles in mechanically ventilated patients. A recent tomographic study also showed a more remarkable atrophy of the diaphragm compared with limb muscles in ICU septic patients.³⁹ However, another report showed 10% atrophy of the rectus femoris in the early course of critical illness,² which may reflect the fact that the rectus femoris is involved in permanent static tone which is abruptly abolished in critical illness. All together, these findings may suggest a major role for inactivity in the pathophysiology of muscle atrophy during critical illness, with a preferential alteration of muscles used for permanent contractions (*e.g.*, diaphragm) or resting tone (*e.g.*, muscles involved in static tone). Interestingly, in our very limited sample ($n = 35$), the use of steroids was strongly associated with pectoral atrophy. Steroids increase protein catabolism^{40,41} and are controversial risk factors for ICU-acquired peripheral weakness.⁴² However, some experimental studies have suggested a possible protective role of steroids against ventilator-induced diaphragm dysfunction *via* inhibition of the calpain system.^{43,44}

Muscular Atrophy and Outcome

We have not found any apparent association between diaphragm atrophy and clinical outcomes in complete cases on day 5 ($n = 35$). However, a significant impact of diaphragm atrophy on mechanical ventilation outcomes has been highlighted in a recent study of much larger sample size.¹⁶ Several factors can explain this discrepancy (*e.g.*, diaphragm thinning or thickening could widely be influenced by the respiratory load endured by the respiratory muscles^{16,29}), and the presence of competing pathologic processes may trigger thickening in opposite directions. In our study, diaphragm thickness was

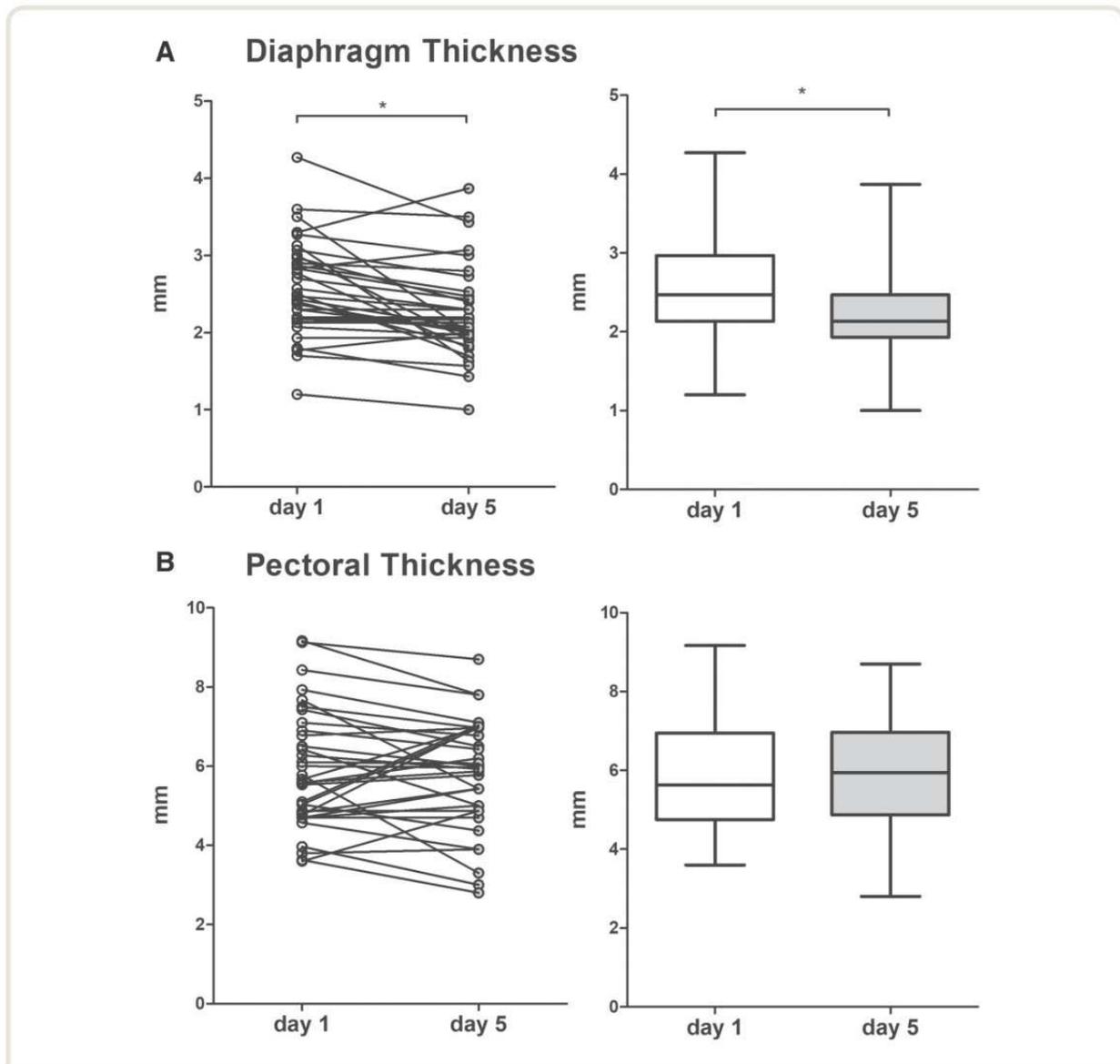


Fig. 5. Diaphragm (A) and pectoral (B) thickness at day 1 and in complete cases on day 5 ($n = 35$). Individual values (*left*) and box plot representation (*right*) for diaphragm thickness (A) and pectoral thickness (B) measurement at day 1 and day 5. Overall, a thinning of the diaphragm was observed between day 1 and day 5, whereas change in pectoral thickness was not significant. * $P < 0.001$ for paired Wilcoxon test for difference between diaphragm thickness at day 1 and day 5.

only ascertained on day 1 and day 5, and we may have failed to detect very early atrophy in many patients. Furthermore, our small sample size did not enable us to adjust associations for important confounders. Unlike diaphragm atrophy, pectoral atrophy was associated with prolonged weaning from mechanical ventilation and a trend toward prolonged ICU stay in our study. A similar association with worse outcomes was previously reported with atrophy of the rectus femoris.² Further studies with bigger sample sizes are needed to depict the respective impacts of diaphragm and peripheral muscles atrophies on the outcomes of critically ill patients.

Strengths and Limitations

The strength of our study lies in the parallel and sequential assessment of diaphragm and pectoral thicknesses by trained sonographers. Our study has several limitations. First, the monocentric design and limited sample size, hence the need for an external validation. Second, the lack of functional test precludes direct extrapolation to respiratory or peripheral muscle weakness. Third, the agreement between observers' measurements is almost proportional to the changes in thickness they measured (*i.e.*, the smaller the change, the lower the

Table 2. Patients Characteristics According to Diaphragm Atrophy at Day 5

	All Patients (n = 35)	Diaphragm Atrophy (n = 17)	No Diaphragm Atrophy (n = 18)	P Value
Age, yr	73 (60 to 80)	74 (55 to 80)	73 (64 to 80)	0.680
Male sex	28 (80%)	12 (71%)	16 (89%)	0.176
BMI, kg/m ²	24 (22 to 28)	23 (21 to 26)	26 (22 to 29)	0.248
Characteristics at inclusion				
SAPS II	57 (43 to 65)	65 (45 to 80)	51 (36 to 57)	0.012
SOFA score	8 (4 to 9)	9 (7 to 11)	6 (2 to 9)	0.013
Lactate, mmol/l	1.7 (1.2 to 4.3)	2.4 (1.4 to 4.7)	1.3 (1.1 to 2.4)	0.072
Sepsis	24 (69%)	14 (82%)	10 (56%)	0.088
Septic shock	14 (40%)	10 (59%)	4 (22%)	0.027
ICU management				
MV	28 (80%)	17 (100%)	11 (61%)	0.008
Sedation	26 (74%)	16 (94%)	10 (55%)	0.018
Length of sedation, h	46 (0 to 78)	46 (19 to 82)	24 (0 to 82)	0.292
Curarization	11 (31%)	6 (35%)	5 (28%)	0.632
Length of curarization, h	0 (0 to 24)	0 (0 to 27)	0 (0 to 29)	0.630
Steroids	13 (37%)	7 (41%)	6 (33%)	0.631
Fluid balance, ml	1,143 (−3,625 to 2,679)	2,705 (−3,936 to 6,467)	−423 (−3,498−1,472)	0.254
Nutritional intake, Kcal	5,900 (3,500 to 7,260)	6,900 (5,552 to 7,525)	4,355 (1,400 to 7,167)	0.070
Duration of parenteral nutrition, h	120 (90 to 120)	120 (75 to 120)	120 (96 to 120)	0.974
Duration of enteral nutrition, h	48 (0 to 96)	96 (2 to 100)	36 (0 to 96)	0.381

Data are n (%) or median (interquartile range). BMI, body mass index; ICU, intensive care unit; MV, mechanical ventilation; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment. Patients were classified according to a threshold of diaphragm atrophy of −10%.

Table 3. Patients Characteristics According to Pectoral Atrophy at Day 5

	All Patients (n = 34)	Pectoral Atrophy (n = 10)	No Pectoral Atrophy (n = 24)	P Value
Age, yr	73 (60 to 80)	68 (64 to 74)	76 (57 to 82)	0.381
Male sex	27 (79%)	9 (90%)	18 (75%)	0.324
BMI, kg/m ²	24 (22 to 28)	22 (19 to 25)	26 (23 to 29)	0.089
Characteristics at inclusion				
SAPS II	55 (43 to 65)	54 (38 to 64)	55 (43 to 65)	0.895
SOFA score	8 (4 to 9)	7 (2 to 9)	8 (4 to 10)	0.285
Lactate, mmol/l	1.7 (1.2 to 4.3)	1.7 (1.2 to 5.3)	1.7 (1.2 to 4.2)	0.925
Sepsis	23 (68%)	5 (50%)	18 (75%)	0.156
Septic shock	13 (38%)	3 (30%)	10 (42%)	0.524
ICU management				
MV	27 (79%)	8 (80%)	19 (79%)	> 0.999
Sedation	25 (73%)	6 (60%)	19 (79%)	0.248
Length of sedation, h	45 (0 to 76)	24 (0 to 96)	45 (4 to 71)	0.867
Curarization	10 (29%)	3 (30%)	7 (29%)	0.961
Length of curarization, h	0 (0 to 24)	0 (0 to 54)	0 (0 to 20)	0.809
Steroids	12 (35%)	7 (70%)	5 (21%)	0.006
Fluid balance, ml	1,143 (−3,625 to 2,579)	−1,422 (−2,705 to 1,324)	1,461 (−4,445 to 3,079)	0.603
Nutritional intake, Kcal	5,900 (3,500 to 7,260)	4,400 (3,905 to 6,180)	6,900 (4,400 to 7,330)	0.179
Duration of parenteral nutrition, h	120 (90 to 120)	120 (105 to 120)	120 (58 to 120)	0.398
Duration of enteral nutrition, h	72 (0 to 96)	72 (24 to 96)	72 (0 to 108)	0.905

Data are n (%) or median (interquartile range). BMI, body mass index; ICU, intensive care unit; MV, mechanical ventilation; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment. Patients were classified according to a threshold of pectoral atrophy of −10%.

agreement), despite our efforts to optimize this reproducibility by using a high-frequency probe and by marking the observation site. Lastly, some factors could theoretically have biased the pectoral thickness measurement, including orientation of the beam, compression of the muscle by the probe, or muscle

infiltration with edema.⁴⁵ Understanding the primary mechanism of ICU-acquired weakness remains a challenge for the intensivists. Our results may help clarify the distinctive patterns of ventilator-induced diaphragm dysfunction and skeletal muscle weakness, which are two outstanding pathologic

entities linked to critical illness myopathy.⁸ Further studies are needed to corroborate these ultrasound results with higher technical accuracy such as computed tomography or magnetic resonance imaging. Gradation and comparative analysis of muscle function and mass could also be of high interest.

Conclusion

Baseline diaphragm thickness was influenced by sex and comorbidities (including chronic obstructive pulmonary disease and diabetes). The diaphragm displayed clinically significant atrophy during the first 5 days of critical illness, especially in patients with septic shock, organ failure, or invasive mechanical ventilation. Given the small sample size, the study did not detect a link between atrophy of the diaphragm and clinical outcomes. Pectoral atrophy seemed confined to patients treated with steroids, and was associated with a poor outcome.

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Competing Interests

The authors declare no competing interests.

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Address correspondence to Dr. Vivier: Service de Réanimation Polyvalente, Hôpital Saint Joseph Saint Luc, 20 Quai Claude Bernard, 69007 Lyon, France. evivier@ch-stjoseph-stluc-lyon.fr. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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Supplemental Table 1. Characteristics of the 97 patients assessed at day-1 according to type of ventilation

	All patients (n=97)	MV (n=62)	SB (n=35)	<i>p</i> value
Age (years)	73 (62, 82)	71 (60, 80)	79 (64, 83)	0.062
Male sex	68 (70%)	44 (71%)	24 (69%)	0.804
BMI (kg.m ²)	24 (21, 29)	24 (22, 29)	24 (21, 29)	0.396
SAPS II at ICU admission	54 (42, 69)	59 (46, 78)	46 (36, 57)	<0.001
SOFA score at ICU admission	6 (4, 9)	8 (5, 9)	4 (2, 6)	<0.001
<i>Comorbidity</i>				
Heart disease	41 (42%)	24 (39%)	17 (49%)	0.395
Hypertension	37 (38%)	21 (34%)	16 (46%)	0.249
Smoking	36 (37%)	23 (37%)	13 (37%)	0.996
COPD	29 (30%)	20 (32%)	9 (26%)	0.499
Diabetes	28 (30%)	16 (26%)	12 (34%)	0.376
<i>Diagnosis at ICU admission</i>				
RCA	7 (7%)	7 (11%)	0 (0%)	0.047
Sepsis	17 (17%)	10 (16%)	7 (20%)	0.630
ARF	31 (32%)	22 (35%)	9 (26%)	0.322
Decompensation of CRI	9 (9%)	4 (6%)	5 (14%)	0.202
Coma	11 (11%)	10 (16%)	1 (3%)	0.048
AKI	7 (7%)	1 (2%)	6 (17%)	0.008
Post,operative	1 (1%)	1 (2%)	0 (0%)	0.450
Other	14 (14%)	7 (11%)	7 (20%)	0.241
Diaphragm thickness (mm)	2.4 (2, 2.9)	2.3 (2, 2.9)	2.7 (2, 3)	0.340
Pectoral thickness (mm)	5.9 (4.7, 7.2)	5.8 (4.7, 7.3)	6 (4.6, 7.1)	0.961

Data are n (%) or median (IQR); MV, mechanical ventilation; SB, spontaneous breathing; BMI, body mass index; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; RCA, recovered cardiopulmonary arrest; ARF, acute respiratory failure; CRI, chronic respiratory insufficiency; AKI, acute kidney injury.

Supplemental Table 2. Characteristics of the 35 patients assessed at day-5 for diaphragm atrophy according to type of ventilation

	All patients (n=35)	MV (n=28)	SB (n=7)	<i>p</i> value
Age (years)	73 (60, 80)	71 (57, 80)	79 (69, 83)	0.087
Male sex	28 (80%)	21 (75%)	7 (100%)	0.300
BMI (Kg.m ²)	24 (22, 28)	24 (22, 27)	28 (17, 29)	0.915
<i>Comorbidity</i>				
Heart disease	14 (40%)	10 (36%)	4 (7%)	0.387
Hypertension	12 (34%)	10 (36%)	2 (29%)	>0.999
Smoking	13 (37%)	10 (36%)	3 (43%)	>0.999
COPD	12 (34%)	10 (36%)	2 (29%)	>0.999
Diabetes	8 (23%)	7 (25%)	1 (14%)	>0.999
<i>Characteristics at inclusion</i>				
SAPS II	57 (43,65)	57 (45,72)	52 (36,59)	0.127
SOFA score	8 (4,9)	8 (6,10)	4 (2,9)	0.027
Noradrenalin	23 (66%)	22 (79%)	1 (14%)	0.004
Lactate (mmol.l ⁻¹)	1.7 (1.2, 4.3)	2.1 (1.3, 4.3)	1.1 (0, 3.5)	0.075
Sepsis	24 (69%)	23 (82%)	1 (14%)	0.002
Septic shock	14 (40%)	13 (46%)	1 (14%)	0.210
<i>Diaphragm thickness</i>				
at day-1 (mm)	2.5 (2.1, 3.0)	2.4 (2.1, 3.0)	2.7 (2.1, 2.9)	0.885
at day-5 (mm)	2.1 (1.9, 2.5)	2.1 (1.9, 2.4)	2.4 (2, 3.1)	0.161
Diaphragm atrophy (%)	-10 (-19, 0)	-11 (-20, 0)	-5 (-8, 8)	0.048
<i>Pectoral thickness</i>				
at day-1 (mm)	5.6 (4.7, 7.0)	5.7 (5, 7.4)	4.7 (3.6,6.3)	0.028
at day-5 (mm)	5.9 (4.9, 7.0)	6.0 (5.0, 7.0)	5.4 (3.9, 7.0)	0.353
Pectoral atrophy (%)	- 3 (-13, 8)	-5 (-12, 5)	3 (-15, 35)	0.403

Data are n (%) or median (IQR); MV, mechanical ventilation; SB, spontaneous breathing; BMI, Body Mass Index; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

Supplemental Table 3A. Outcome of 35 patients assessed for diaphragm atrophy at day-5

Patients outcome	All patients (n=35)	Diaphragm atrophy (n=17)	No diaphragm atrophy (n=18)	p value
Successful weaning from MV [#]	43% (12/28)	41% (7/17)	45% (5/11)	0.823
Discharged alive from ICU [§]	51% (18/35)	35% (6/17)	67% (12/18)	0.063
Discharged alive from hospital [§]	34% (12/35)	29% (5/17)	39% (7/18)	0.555

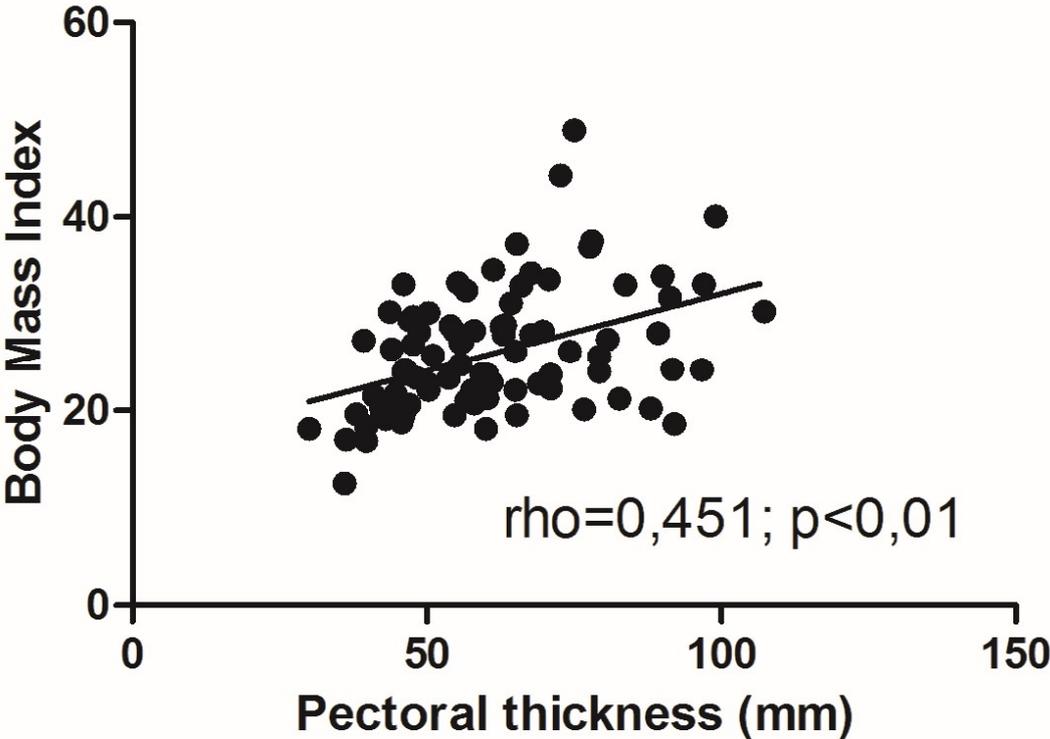
MV, mechanical ventilation; ICU, intensive care unit; Outcomes were assessed at day-14[#] and day-28[§] after admission. 35 patients were followed from day-1 to day-5[§] including 28 patients ventilated[#]. Patients were classified according to a threshold of diaphragm atrophy of -10%.

Supplemental Table 3B. Outcome of 34 patients assessed at day-5 for pectoral atrophy

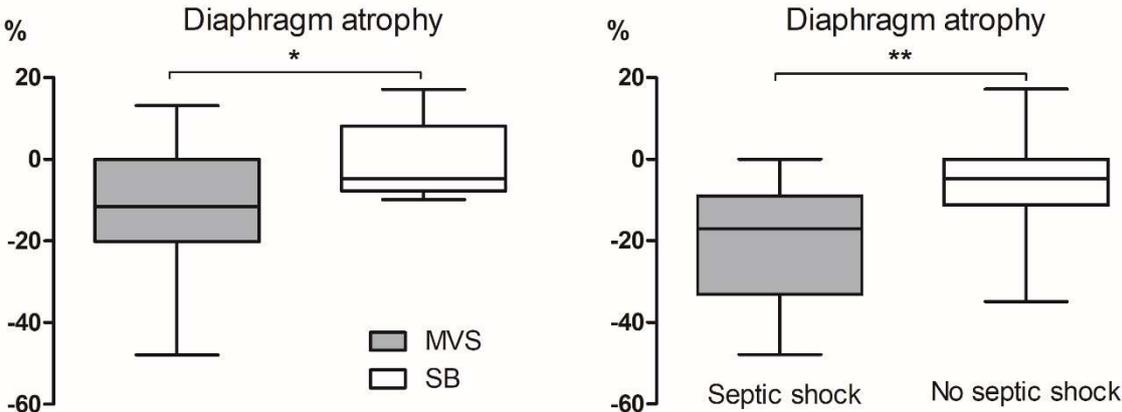
Patients outcome	All patients (n=34)	Pectoral atrophy (n=10)	No pectoral atrophy (n=24)	p value
Successful weaning from MV [#]	44% (12/27)	12% (1/8)	58% (11/19)	0.043
Discharged alive from ICU [§]	53% (18/34)	30% (3/10)	62% (15/24)	0.084
Discharged alive from hospital [§]	35% (12/34)	20% (2/10)	42% (10/24)	0.228

MV, mechanical ventilation; ICU, intensive care unit; Outcomes were assessed at day-14[#] and day-28[§] after admission. 35 patients were followed from day-1 to day-5[§] including 28 patients ventilated[#]. Patients were classified according to a threshold of pectoral atrophy of -10%.

Supplemental Figure 1. Correlation between pectoral thickness and body mass index



Supplemental Figure 2. Diaphragm atrophy versus respiratory conditions or septic shock.



Travail n°3

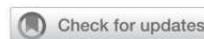
Inability of Diaphragm Ultrasound to Predict Extubation Failure:

A Multicenter Study.

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Inability of Diaphragm Ultrasound to Predict Extubation Failure

A Multicenter Study



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BACKGROUND: Diaphragmatic dysfunction may promote weaning difficulties in patients who are mechanically ventilated.

OBJECTIVE: The goal of this study was to assess whether diaphragm dysfunction detected by ultrasound prior to extubation could predict extubation failure in the ICU.

METHODS: This multicenter prospective study included patients at high risk of reintubation: those aged > 65 years, with underlying cardiac or respiratory disease, or intubated > 7 days. All patients had successfully undergone a spontaneous breathing trial. Diaphragmatic function was assessed by ultrasound prior to extubation while breathing spontaneously on a T-piece. Bilateral diaphragmatic excursion and apposition thickening fraction were measured, and diaphragmatic dysfunction was defined as excursion < 10 mm or thickening < 30%. Cough strength was clinically assessed by physiotherapists. Extubation failure was defined as reintubation or death within the 7 days following extubation.

RESULTS: Over a 20-month period, 191 at-risk patients were studied. Among them, 33 (17%) were considered extubation failures. The proportion of patients with diaphragmatic dysfunction was similar between those whose extubation succeeded and those whose extubation failed: 46% vs 51% using excursion ($P = .55$), and 71% vs 68% using thickening ($P = .73$), respectively. Values of excursion and thickening did not differ between the success and the failure groups: at right, excursion was 14 ± 7 mm vs 11 ± 8 ($P = .13$), and thickening was $29 \pm 29\%$ vs $38 \pm 48\%$ ($P = .83$), respectively. Extubation failure rates were 7%, 22%, and 46% in patients with effective, moderate, and ineffective cough ($P < .01$). Ineffective cough was the only variable independently associated with extubation failure.

CONCLUSIONS: Diaphragmatic dysfunction assessed by ultrasound was not associated with an increased risk of extubation failure. CHEST 2019; 155(6):1131-1139

KEY WORDS: diaphragm; ultrasound; weaning

ABBREVIATION: SBT = spontaneous breathing trial

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In an ICU, the decision regarding extubation is of critical importance because mortality is particularly high in cases of reintubation.¹ Notwithstanding application of weaning criteria, the overall rate of reintubation following planned extubation is approximately 10% to 15%.² A spontaneous breathing trial (SBT) is the best way to assess readiness for extubation of intubated patients in the ICU,³ and guidelines recommend a systematic SBT before extubation in all patients intubated for at least 24 h.⁴ However, even after having successfully undergone an SBT, reintubation rates may exceed 20% in patients most at-risk.⁴⁻⁶ Although the reasons for reintubation may often be multifactorial due to respiratory or cardiac failure, upper airway obstruction, inability to clear secretions, or neurologic disorders, another reason could be latent diaphragm dysfunction.

Although the magnetic stimulation of the phrenic nerve is considered the reference method for detecting

diaphragm dysfunction, this approach is not feasible in daily ICU practice at bedside.⁷ Diaphragm ultrasound, which allows direct diaphragm visualization, has been proposed to assess patient inspiratory effort during the weaning period.⁸⁻¹¹ Several studies have found that low excursion or weak diaphragm apposition thickening was strongly associated with weaning difficulties in patients who are mechanically ventilated, leading to prolonged mechanical ventilation.¹¹⁻¹³ The most recent studies have even suggested that diaphragm ultrasound enabled the prediction of extubation outcome.¹³⁻¹⁵ However, these studies were all performed in single centers with small patient samples, and ultrasound was not systematically applied just prior to extubation.^{13,14} With these factors in mind, we conducted a large prospective multicenter study aimed at assessing whether diaphragm dysfunction detected by ultrasound just at time of extubation was associated with extubation failure in at-risk patients who have successfully undergone an SBT.

Methods

Detailed methods are provided in e-Appendix 1.

Study Design and Patients

This observational prospective study was conducted between March 2015 and October 2016 in three French ICUs. The study was approved by the French Ethics Committee CPP Sud-Est II.

Patients at high-risk of reintubation (ie, aged > 65 years, with any underlying cardiac or chronic lung disease, or intubated > 7 days prior to extubation^{5,6}) were eligible for the study if they fulfilled all the weaning criteria (e-Appendix 1) and had successfully undergone an SBT. Clinical assessment of peripheral and respiratory muscle strength, as well as amount of secretions, was performed by a physiotherapist prior to extubation. Inability to manage secretions that may lead to postponed extubation was considered in patients with both ineffective cough and abundant secretions. Following the decision to extubate that was made by the clinician, all included patients underwent spontaneous breathing on a T-piece to perform bilateral diaphragm ultrasound recordings and spirometric measurements; the patients were then systematically extubated. Prophylactic noninvasive ventilation could be applied immediately following planned extubation and continued for up to 48 h to avoid acute respiratory failure, especially in patients with hypercapnia.

The primary end point was extubation failure, defined as reintubation or death within the 7 days following planned extubation. The secondary outcome was occurrence of a respiratory failure episode within the first 48 h following planned extubation requiring reintubation, noninvasive ventilation, or high-flow oxygen therapy as a therapeutic measure to treat respiratory failure.

Results

Study Population

Over a 20-month period, 1,319 patients ready for extubation were screened, 284 patients at high risk of

Ultrasound, Clinical, and Spirometric Assessments

Measurements were systematically performed in patients breathing spontaneously through a T-piece without any ventilator assistance. Excursion of the diaphragm dome and thickening of the diaphragm zone of apposition were recorded in M-mode by using a 4-MHz linear probe and a 10-MHz linear probe, respectively, as previously described (e-Appendix 1).¹²⁻¹⁶ In accordance with the literature, diaphragm dysfunction was defined as excursion < 10 mm¹³ or weak thickening < 30%¹⁴ of at least one hemidiaphragm.

Strength of limb muscles¹⁷ and cough strength were clinically assessed prior to extubation by physiotherapists. Cough was scored by using a semi-objective scale^{6,18} and was classified as ineffective, moderate, or effective. Sputum amount was quantified, scored, and then dichotomized as mild or abundant.

Spirometric measurements were performed under spontaneous breathing conditions enabling successive evaluation of the rapid shallow breathing index, vital capacity, peak cough expiratory flow, maximum inspiratory pressure, and maximum expiratory pressure.¹⁹

Statistical Analysis

Continuous variables are expressed as mean \pm SD or median (25th-75th percentiles), and qualitative variables are expressed as number and percentage. Continuous variables were compared by using the Student *t* test or the Mann-Whitney *U* test according to the distribution, and categorical variables were compared with the χ^2 test or Fischer exact test as appropriate. Variables associated with extubation failure were assessed by means of multivariate logistic regression analysis.

reintubation were eligible, and 191 were included in the study (e-Fig 1). Their characteristics are detailed in Table 1. Of the 191 patients, 28 developed severe acute respiratory failure within the first 48 h following extubation, including 22 patients who needed early

reintubation and six patients who were successfully treated with a noninvasive strategy of oxygenation (noninvasive ventilation or high-flow oxygen therapy). Eight additional patients needed reintubation within the first 7 days following extubation (30 patients were reintubated in total), and three additional patients died without reintubation within the first week due to a do-not-reintubate order decided between extubation and day 7. Thus, 33 patients (17%) were considered as experiencing

extubation failure at day 7 (primary end point). The main reasons for reintubation were hypoxia (n = 9), inability to clear secretions (n = 8), hypercapnia (n = 3), upper airway obstruction (n = 2), shock (n = 7), and altered consciousness status (n = 1).

TABLE 1] Characteristics of the 191 Study Patients

Age, y	68 ± 4
Male sex	121 (63%)
BMI, kg/m ²	28 ± 6
SAPS II at admission, points	48 ± 18
Duration of mechanical ventilation prior to extubation, d	5 (2-10)
Medical condition	
Coronary heart disease	52 (27%)
Valvular heart disease	21 (11%)
Atrial fibrillation	37 (19%)
Left ventricular systolic dysfunction	38 (20%)
COPD	36 (19%)
Restrictive lung disease	15 (8%)
Reason for intubation	
Acute respiratory failure	76 (40%)
Shock	42 (22%)
Coma	29 (15%)
Cardiac surgery	23 (12%)
Cardiac arrest	11 (6%)
Other	10 (5%)
Clinical assessment	
MRC score	44 ± 15
Abundant sputum	33/173 (19%)
Cough strength	
Ineffective (0-1)	13/181 (7%)
Moderate (2-3)	101/181 (56%)
Effective (4)	67/181 (37%)
Clinical outcomes	
Postextubation severe respiratory failure at 48 h	28 (15%)
Reintubation at day 7	30 (16%)
Reintubation or death at day 7	33 (17%)
Length of ICU stay, d	10 (5-20)
ICU mortality	16 (8%)

Data are presented as presented as mean ± SD or median (interquartile range), and categorical variables are presented as No. (%). MRC = Medical Research Council; SAPS II = Simplified Acute Physiology Score II.

Ultrasound and Clinical Assessment

Diaphragm excursion could be measured in 189 patients on the right side (99% of cases) and in 160 patients on the left side (84% of cases), presenting a mean value of 13 ± 7 mm at right and 14 ± 7 mm at left. Measurement of diaphragm thickening could be measured in 164 patients at right (86% of cases) and 146 patients at left (76% of cases), presenting mean thickening of 30% (±33) at right and 34% (±40) at left.

Among the 189 patients who had at least one measurement of diaphragm excursion, 88 (47%) exhibited diaphragm dysfunction with excursion < 10 mm on at least one side. Bilateral dysfunction was found in 12.5% of the patients (20 of 160 patients who had bilateral assessment of diaphragm excursion). A paradoxical inspiratory ascent of hemidiaphragm was detected in five patients at right and in one patient at left.

Among the 182 patients who had at least one measurement of diaphragm thickening, 128 (70%) exhibited diaphragm dysfunction with thickening < 30% on at least one side. Bilateral dysfunction was found in 47% of the patients (60 of 127 patients who underwent bilateral assessment of diaphragm thickening). Paradoxical inspiratory thinning of diaphragm was detected in seven patients at right and 11 patients at left.

ICU-acquired weakness was diagnosed in 50% of the patients at time of extubation (89 of 178 cooperating patients). Among 181 patients who could have clinical cough strength assessment, cough was considered ineffective in 13 patients (7%), moderate in 101 (56%), and effective in 67 (37%). Cough peak expiratory flow measurements and clinical cough strength assessment were weakly but significantly correlated ($\rho = 0.28$; $P < .01$).

Factors Associated With Extubation Failure

Diaphragm excursion or thickening at right or at left did not differ between patients who were successfully extubated and those who needed reintubation or died within the 7 days following extubation (Figs 1, 2, Table 2). The proportion of patients with diaphragmatic

dysfunction was similar between those who succeeded in extubation and those who failed: 71% vs 68% using thickening of the diaphragm ($P = .73$) and 46% vs 51% using excursion of the diaphragm ($P = .55$), respectively. Performance of diaphragm ultrasound thresholds to detect extubation failure at day 7 is detailed in e-Table 1, but no other threshold appears more relevant (e-Figs 2, 3). Moreover, diaphragm excursion or thickening at right or at left did not differ between patients who developed severe acute respiratory failure within the 48 h following extubation compared with the other patients (e-Table 2).

No spirometric measurements were associated with extubation failure, and cough peak expiratory flow did not differ between patients whose extubation failed and other patients (Table 2). Patients who failed extubation were less likely to have effective cough clinically assessed by physiotherapists and more frequently had ICU-acquired weakness compared with those who were successfully extubated. Extubation failure rates were 7%, 22%, and 46% in patients with effective, moderate, and ineffective cough, respectively ($P < .01$) (Fig 3). Multivariate logistic regression analysis showed that effective cough was the only factor independently associated with extubation success at day 7: OR, 0.30; 95% CI, 0.14-0.67; $P < .01$ (e-Table 3).

Discussion

At time of extubation, approximately 50% of patients had low diaphragm excursion (< 10 mm) and around 70% had weak diaphragm thickening ($< 30\%$), suggesting diaphragm dysfunction. We found that neither low diaphragm excursion nor weak diaphragm

thickening was associated with reintubation or death within the 7 days following extubation. Clinical assessment of cough strength was the only predictor of extubation outcome.

Impact of Diaphragm Dysfunction on Extubation Outcome

The diffusion and improvement of ultrasound techniques over the last 15 years have rendered it possible to explore diaphragm movement at bedside in ICU patients.^{8,20} Detection of decreased dome excursion (< 10 mm)¹³ or decreased thickening of the zone of apposition ($< 30\%$)^{11,12,14} have been proposed as surrogates for detecting a decrease in depression produced by the diaphragm as a consequence of diaphragm dysfunction. To date, several studies have reported that diaphragm dysfunction assessed via ultrasound was particularly frequent during the weaning period, involving from 30% to 70% of ICU patients.¹¹⁻¹³ This diagnosis was deemed associated with SBT failure^{21,22} and prolonged weaning prior to extubation.^{11,12} However, few studies have specifically assessed the impact of diaphragm dysfunction on extubation outcome proper.¹³⁻¹⁵ These single-center studies included small patient samples and did not assess diaphragmatic function according to a standardized procedure. Measurements were not systematically conducted at time of extubation and could have been performed during spontaneous breathing or pressure support ventilation.¹⁴ Definition of extubation failure was heterogeneous and included patients who had failed SBT and were not extubated, those extubated for end of life, or those who had developed an acute respiratory failure episode.^{13,14}

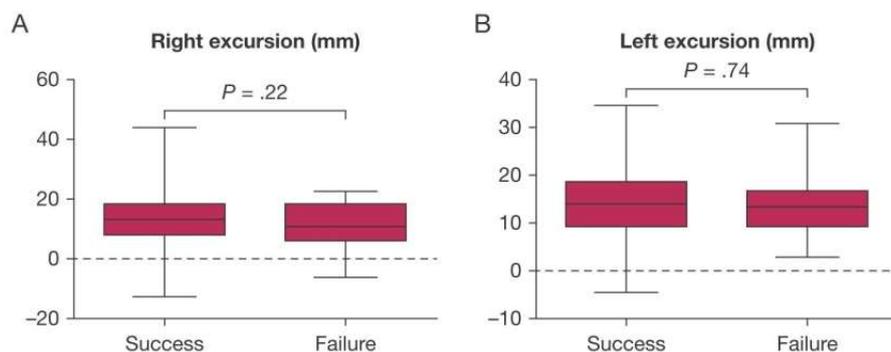


Figure 1 – Right (A) and left (B) diaphragm excursion according to extubation outcome at day 7. The right and left excursion of the diaphragm are presented here for each group (success or failure) by a box plot representation with median, 25th and 75th percentiles, and adjacent values. There was no significant difference between patients whose extubation succeeded and those whose extubation failed. Negative values reflect paradoxical movements (passive ascent) associated with complete hemidiaphragm paralysis.

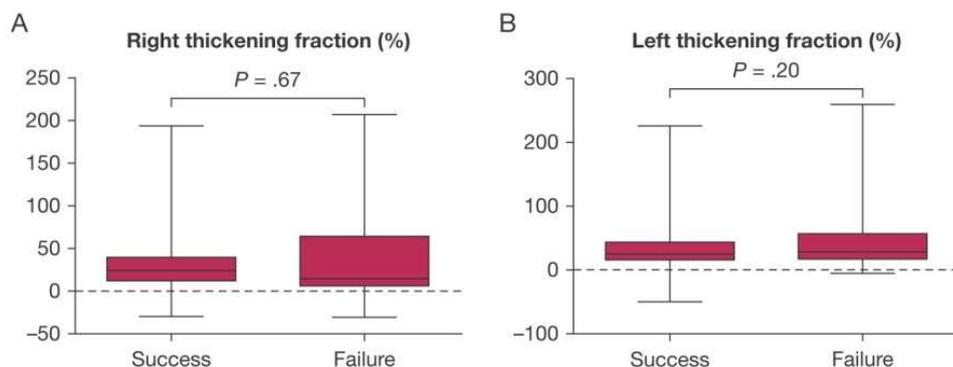


Figure 2 – Right (A) and left (B) diaphragm thickening according to extubation outcome at day 7. The right and left thickening of the diaphragm are presented here for each group (success or failure) by a box plot representation with median, 25th and 75th percentiles, and adjacent values. There was no significant difference between patients whose extubation succeeded and those whose extubation failed. Negative values reflect paradoxical movements (passive thinning) associated with complete hemidiaphragm paralysis.

Unlike these previous studies, we included only patients who had successfully undergone an SBT and were considered ready to be extubated.³ We found that assessment of diaphragm function by ultrasound while breathing spontaneously just prior to extubation did not enable prediction of extubation outcome using either bilateral excursion or thickening of the diaphragm. This result raises two hypotheses: either our definition of accuracy in detecting diaphragm dysfunction by ultrasound is flawed, or diaphragm weakness is not an overriding factor in determining extubation failure.

Risk Factors for Extubation Failure

In the present study, patients intubated > 7 days prior to extubation and those with underlying chronic cardiac disease had lower reintubation rates than the other patients. The reasons could be that patients with prolonged mechanical ventilation were markedly younger than the other patients (58 ± 15 years vs 73 ± 9 years; $P < .001$) and that nearly one-fourth of patients with any underlying cardiac disease were included following cardiac surgery, and none of them needed reintubation. Nevertheless, none of these factors was independently associated with extubation failure according to multivariate logistic regression analysis.

Assessment of respiratory muscle functions by using volumetric or pressure indexes did not predict extubation failure. Although some studies have found that vital capacity,^{23,24} maximal inspiratory pressure,²⁴ or rapid shallow breathing index²⁵ may help to predict extubation outcome, others have found that spirometric measurements are poor predictors of

extubation failure²⁶ and that the rapid shallow breathing index should be interpreted with caution depending on clinical setting²⁷ in view of avoiding delayed extubation.²⁸

Following multivariate analysis, ineffective cough was the only factor that remained independently associated with extubation failure. This result is in keeping with a previous study showing that clinically assessed ineffective cough was a stronger predictor of extubation failure than ICU-acquired weakness.⁶ In contrast, as has been found in other studies,²⁹⁻³¹ cough strength measured via spirometer using peak cough expiratory flow was not associated with extubation failure. In the present study, dynamic assessment by physiotherapists seemed to be more efficient than a one-off measure with the spirometer.

Clinical Implications for Extubation

Understanding the pathophysiology of weaning failure is essential, given the impact of extubation failure on ICU patient outcomes.³² However, successful weaning from the ventilator does not imply successful extubation proper. This last step depends on specific physiological factors, among which diaphragmatic dysfunction may play only a minor role. It has been well demonstrated that a decision to extubate in the ICU should be made as soon as all weaning criteria are met and the patient has successfully passed an SBT.^{33,34} Our findings do not support either systematic exploration of the diaphragm with ultrasound or systematic spirometric measurements, which could be time-consuming and needlessly delay extubation. Our results are not contradictory, with studies showing that diaphragm dysfunction may prolong mechanical

TABLE 2] Comparison of Patients Who Had a Successful Extubation and Those Who Failed and Needed Reintubation or Died Within the First 7 Days Following Extubation (N = 191)

Variable	Extubation Success (n = 158 [83%])	Extubation Failure (n = 33 [17%])	P Value
Age, y	67 ± 14	70 ± 15	.17
Male sex	102 (65%)	19 (58%)	.45
BMI, kg/m ²	28 ± 7	26 ± 5	.29
SAPS II at admission, points	46 ± 18	55 ± 18	.01
Duration of MV prior to extubation, d	5 (2-10)	5 (3-7)	.78
Use of prophylactic NIV	63 (39%)	16 (53%)	.15
Risk factor for extubation failure			
Age > 65 y	99 (63%)	25 (76%)	.15
Mechanical ventilation > 7 d	67 (42%)	8 (24%)	.05
Underlying chronic cardiac disease	84 (53%)	11 (33%)	.04
Underlying chronic lung disease	48 (30%)	7 (21%)	.29
Clinical assessment			
MRC score, points	46 ± 14	38 ± 15	< .01
MRC score < 48	66/146 (45%)	23/32 (72%)	< .01
Abundant sputum	27/147 (18%)	6/32 (19%)	.96
Cough strength			< .01
Ineffective (0-1)	7/148 (5%)	6/33 (18%)	
Moderate (2-3)	79/148 (53%)	22/33 (67%)	
Effective (4)	62/148 (42%)	5/33 (15%)	
Spirometric measurements			
Respiratory rate, min ⁻¹	27 ± 7	29 ± 9	.43
Tidal volume, mL	375 ± 134	354 ± 104	.73
Vital capacity, mL	1142 ± 522	978 ± 480	.09
Maximal inspiratory pressure, cm H ₂ O	-42 ± 16	-44 ± 19	.80
Maximal expiratory pressure, cm H ₂ O	50 ± 24	50 ± 26	.98
Cough peak expiratory flow, L/min	61 ± 24	58 ± 22	.41
CPEF ≤ 35	12/132 (9%)	2/28 (7%)	.74
CPEF ≤ 60	74/132 (56%)	18/28 (64%)	.42
Rapid shallow breathing index, breaths/min/mL	81 ± 43	88 ± 49	.51
f/V _T > 105	32/112 (29%)	10/28 (36%)	.46
Ultrasonographic measurements			
Diaphragm excursion			
Right, mm	14 ± 7	11 ± 8	.22
Right EXdi < 10 mm	50/156 (32%)	14/33 (42%)	.25
Left, mm	14 ± 7	14 ± 6	.74
Left EXdi < 10 mm	36/130 (28%)	8/30 (27%)	.91
Diaphragm thickness			
Right, mm	2.5 ± 1.1	2.7 ± 1.0	.19
Left, mm	2.5 ± 1.0	2.7 ± 1.1	.31
Diaphragm thickening			
Right, %	29 ± 28	36 ± 48	.67
Right TFdi < 30%	85/134 (63%)	18/30 (60%)	.72

(Continued)

TABLE 2] (Continued)

Variable	Extubation Success (n = 158 [83%])	Extubation Failure (n = 33 [17%])	P Value
Left, %	31 ± 34	50 ± 60	.20
Left TFdi < 30%	71/120 (59%)	14/26 (54%)	.62

Continuous variables are presented as mean ± SD or median (interquartile range), and categorical variables are presented as absolute value (%). CS = cough strength; CPEF = cough peak expiratory flow; f/V_T = respiratory rate divided by tidal volume; EXdi = excursion of the diaphragm; MV = mechanical ventilation; NIV = noninvasive ventilation; TFdi = thickening fraction of the diaphragm. See Table 1 legend for expansion of other abbreviations.

ventilation and delay extubation.³⁵ Diaphragm ultrasound may be useful early in the weaning process to identify the mechanism explaining SBT failure.^{11,12} However, the success of SBT relies on ensuring that diaphragm function is adequate for spontaneous breathing. Once a trial is successful, the diaphragm may no longer be a determinant for extubation failure, which may be more clearly anticipated by the inability to clear secretions with effective cough. Our main finding is that clinicians should spend more time assessing airway protection and cough rather than diaphragm function in patients who have successfully passed an SBT.

Study Limitations

This study had several limitations. First, diaphragm ultrasound index performance is weakened by major variability. The usual agreement limit of diaphragm excursion in quiet breathing has been reported to be about 2.5 mm,¹⁶ whereas the agreement limit of diaphragm thickening is up to 20%.^{36,37} Moreover, probable underestimation of anatomic variations of diaphragm insertion, which involves up to 15% of patients,^{38,39} may have interfered with the exactness of the diaphragm thickness assessment.

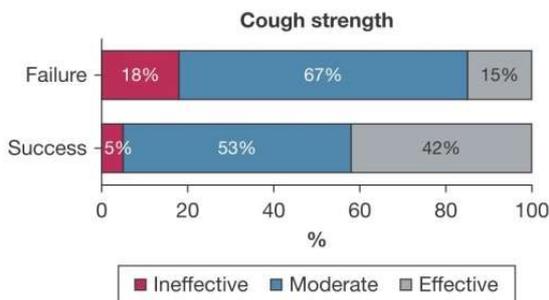


Figure 3 – Cough strength according to extubation outcome at day 7. Patients who failed extubation were more likely to have ineffective cough than the others (18% vs 5%; $P < .01$) and less likely to have effective cough (15% vs 42%; $P < .01$).

Second, the amplitude of diaphragm excursion and thickening is highly dependent on load conditions. We assessed diaphragm function during spontaneous breathing just prior to extubation in all patients, which was not the case in any of the previous studies.¹³⁻¹⁵ Slight thickening may be the expression of several distinct factors such as intrinsic weakness of the muscle, residual sedation, or simply the absence of necessary ventilatory effort (in case of quiet breathing).⁴⁰ These entangled factors could contribute to the lack of conclusive results. As previously suggested, recording maximal thickening (from residual volume to total lung capacity) could be more accurate than tidal thickening in estimating diaphragm strength.²¹ However, the feasibility of such a measurement has not been evaluated in a large group of patients and assumes good patient cooperation.

Third, we were unable to compare ultrasound findings vs a standard diagnostic technique for diaphragm dysfunction, such as magnetic stimulation of the phrenic nerve. One study¹² reported correlations between diaphragmatic contractility measured by using magnetic twitch stimulation of the phrenic nerves (operational gold standard) and ultrasound imaging of the diaphragm.

Lastly, prophylactic noninvasive ventilation during the postextubation period was not systematically applied in all study patients, which may have biased the extubation outcome by concealing diaphragm dysfunction repercussions. However, noninvasive ventilation was not found in this study to be associated with a decreased risk of extubation failure, which probably mitigates the impact of noninvasive ventilation on the results.

Conclusions

Following the success of an SBT, assessment of diaphragm function by ultrasound prior to extubation did not enable prediction of extubation outcome in patients at high risk of reintubation in the ICU. By contrast, clinical assessment of cough strength was found to be a strong predictor of extubation failure.

Acknowledgments

Author contributions: E. V. and A. W. T. designed the study. E. V. coordinated the study. E. V., M. M., J.-B. P., J. S., S. B., G. B., F. B., A. L., C. P., and A. W. T. were responsible for patient screening, enrollment, and follow-up. E. V./J.-B. P., E. V./M. M., and A. W. T./F. B. performed blind and off-line analyses of the ultrasound study in Lyon, Annecy, and Poitiers, respectively. E. V., M. M., and A. W. T. analyzed the data. E. V., M. M., J.-B. P., G. B., F. B., and A. W. T. wrote the manuscript. A. M.-D. critically proofread the manuscript. All authors had full access to all of the study data, contributed to drafting the manuscript or critically revised it 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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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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Inability of Diaphragm Ultrasound to Predict Extubation Failure

A Multicenter Study

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e-Appendix 1.

Methods

Study design and patients

We conducted an observational prospective study between March 2015 and October 2016 in three French Intensive Care Units. The study was approved by the independent ethics committee of Lyon (French Ethics Committee CPP Sud-Est II) and registered at <http://www.clinicaltrials.gov> with the following identification number: NCT02883465.

Patients at high-risk of reintubation, *i.e.* aged more than 65 years old, with any underlying cardiac or chronic lung disease, or intubated more than 7 days prior to extubation^{1,2} were eligible for the study if they fulfilled all the weaning criteria according to our weaning protocol (see below) and had successfully undergone a SBT. Underlying cardiac disease included left ventricular systolic dysfunction, ischemic cardiopathy, chronic atrial fibrillation or severe valvular dysfunction, whereas underlying respiratory disease included chronic obstructive pulmonary disease, obesity-hypoventilation syndrome or rib cage abnormalities. Patients intubated less than 24 hours, with underlying chronic neuromuscular disease, drains or post-operative dressings impairing the ultrasound window, or do-not-reintubate order at time of extubation were excluded. Patients were first informed verbally of the study. Later, information leaflets were given to them or to their relatives, according to the clinical evolution. They were free to accept or refuse participation at any time.

Weaning procedure

A spontaneous breathing trial was systematically performed with T-piece or low levels of pressure-support (PS 7 cmH₂O) without positive end-expiratory pressure for 1 hour as soon as the patient met all of the following criteria³: respiratory rate \leq 35 breaths per minute, adequate oxygenation defined SpO₂ > 90% with FiO₂ \leq 0.4 or PaO₂/FiO₂ > 150 mm Hg with positive end-expiratory pressure (PEEP) \leq 8 cmH₂O, patient awake with a Richmond Agitation-Sedation Scale between +1 and -2,³ no continuous sedation, and no need for vasopressors.

Failure of spontaneous breathing trial was defined according to the usual criteria from the international conference consensus on weaning as the development during the trial of any of the following events: respiratory rate > 35 breaths/min, increased accessory muscle activity, SpO₂ persistently below 90% (on

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FiO₂ 0.4 or at least 6 L/min of oxygen), heart rate persistently above 140 beats / min, systolic blood pressure < 90 or > 180 mmHg, or appearance of cyanosis or mottling, depressed mental status or agitation.

Clinical assessment of peripheral and respiratory muscle strength, and amount of secretions was performed by a physiotherapist before extubation. Inability to manage secretions that may lead to postponed extubation was considered in patients with both ineffective cough and abundant secretions. After the decision to extubate was made by the clinician, all included patients underwent spontaneous breathing on T-piece to perform bilateral diaphragm ultrasound recordings and spirometric measurements, and were then systematically extubated.

Procedure for assessment of diaphragmatic function using ultrasound

Diaphragm ultrasound images were acquired by trained investigators with either Vivid S6 (General Electric Healthcare, Little Chalfont, Buckinghamshire, England) or CX-50 (Philips Ultrasound, Bothell, WA, USA). Measurements were systematically performed in patients in a semi-recumbent position after at least ten minutes of spontaneous breathing through a T-piece without any ventilator assistance. Diaphragm excursion (Exdi) was recorded in M-mode using a 4 MHz linear probe. Right and left hemidiaphragm excursions were measured by placing the probe under the right and left subcostal area and targeting the beam towards the highest point of the dome⁴. As the subcostal technique has frequently been ineffective in the left side because of stomach or colic air interposition, a midaxillary approach was often practiced and corrected by anatomic mode⁵. Diaphragm thickening was recorded on bilateral zone of apposition, as previously.⁶ A 10 MHz linear probe was placed on the 9-10th intercostal space perpendicularly to the chest wall. Diaphragm was recognized as the hypoechoic structure framed by both hyperechoic lines of pleural and peritoneal membranes. Recordings of diaphragm thickness modulation with breathing cycles were acquired in M-mode. The sweep speed was adjusted as slowly as possible to obtain a minimum of three cycles on the same image. A subsequent blind analysis of the all records allowed for measurement of the indexes. All measurements (thickening and excursion) were performed on three successive cycles and averaged. Diaphragm excursion (Exdi) was measured for each hemidiaphragm as the maximal distance between dome position at inspiration and at expiration.⁷ Diaphragm thickening fraction (TFdi) was calculated for each side as the difference [end inspiratory thickness minus end expiratory thickness] divided by end expiratory thickness and expressed as percentage.⁸ In accordance with the literature, diaphragm dysfunction was defined as excursion lower than 10 mm⁹ or weak thickening lower than 30%¹⁰. As we performed bilateral measurements diaphragmatic dysfunction was considered in case of dysfunction of at least one hemidiaphragm. All ultrasound recordings were analyzed off-line and blind to

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the outcomes by two trained investigators in each center (EV/JBP in Lyon, EV/MM in Annecy and FB/AWT in Poitiers).

Clinical and spirometric assessment

After verifying the patient's cooperation, strength of limb muscles was assessed by the physiotherapist using the Medical Research Council (MRC) score; ICU-acquired paresis was defined as a MRC score below 48 points.¹¹ Cough strength just before extubation was clinically assessed by physiotherapists and scored using a semi-objective scale, as previously validated^{1,12,13}. It was graded as 0 (absent), 1 (ineffective), 2 (weak), 3 (moderate), or 4 (strong), and then classified as "ineffective" for a score from 0 to 1, "moderate" for a score from 2 to 3 and "effective" for a score of 4. Sputum amount was quantified and scored from 0 to 4 according to the following criteria; 0 (absence); 1 (slight); 2 (moderate); 3 (abundant); 4 (very abundant) and then dichotomized as "abundant" for a score of 3 to 4.

Spirometric measurements were performed under spontaneous breathing conditions with a portable monitor (FluxMed GrH, MBMED, Buenos Aires, Argentina) connected to the endotracheal tube. The five following sequences methodically unfolded: one minute of quiet ventilation, three maximal inspirations from residual volume to vital capacity, three forced inspirations against occlusion, three forced expirations against occlusion, and a provoked cough salve. Maximal inspiratory pressure was the most negative pressure generated by the patient during a maximal inspiratory effort against an occluded one-way valve following a maximal expiratory maneuver.¹⁴ The valve allowed exhalation and ensured that inspiratory efforts started at low lung volumes (residual volume). A subsequent blind analysis of the curves made it possible to measure for each patient the rapid shallow breathing index, vital capacity, maximum inspiratory pressure, maximum expiratory pressure and peak cough expiratory flow.

Extubation outcome

The primary endpoint was extubation failure defined as reintubation or death within the 7 days following planned extubation. The secondary outcome was occurrence of a respiratory failure episode within the first 48 hours after planned extubation requiring reintubation, non-invasive ventilation or high-flow oxygen therapy as a therapeutic measure to treat respiratory failure.

The following prespecified criteria were used for endotracheal intubation: cardiac or respiratory arrest; hemodynamic failure defined as systolic arterial pressure < 90 mm Hg or mean arterial pressure < 65 mm

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Hg with the need for vasopressors; altered consciousness or coma; respiratory failure defined by at least 2 criteria among the following: (1) respiratory rate > 35/min, (2) clinical signs suggesting respiratory distress with increase in the work of breathing and/or respiratory fatigue including activation of accessory respiratory muscles, (3) respiratory acidosis defined as pH < 7.35 units and PaCO₂ > 45 mm Hg, (4) hypoxemia defined as SpO₂ < 92% despite FiO₂ 0.8 or PaO₂/FiO₂ < 100 mm Hg.

Prophylactic non-invasive ventilation could be applied immediately after planned extubation and continued for up to 48 hours to avoid acute respiratory failure, especially in hypercapnic patients.^{15,16}

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median [25th-75th percentiles], and qualitative variables were expressed as number and percentage. Continuous variables were compared using the Student t-test or the Mann-Whitney U test according to the distribution, or the Kruskal-Wallis test (more than two samples comparison) and categorical variables were compared with Chi-square test or Fischer's exact test as appropriate. The Spearman correlation was used to test the relationship between Exdi and TFdi and between cough peak expiratory flow and clinically assessed cough strength. Variables associated with extubation failure were assessed by means of multivariate logistic-regression analysis. Variables associated with the outcome with a p < 0.10 after univariate analysis were entered into the maximal model. Kaplan-Meier curves were plotted to assess extubation failure in patients with ICU-acquired paresis or ineffective cough versus the others, and compared by the log-rank test. A two-tailed P-value of less than 0.05 was considered as statistically significant. Statistical analyses were performed with SPSS, v.20 (IBM, Chicago, Illinois, USA).

Sample size calculation

Based on a prevalence of diaphragm dysfunction of 50% and an overall rate of extubation failure around 20%, we determined that enrollment of 164 patients would provide a power of 90% to show an absolute increased in extubation failure rate from 10% in patients without diaphragm dysfunction to 30% in those with diaphragm dysfunction at a two-sided alpha level of 0.05. Given potential difficult measurement of diaphragm ultrasound we planned to include 10% more and to enroll around 180 patients in total.

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e-Table 1. Performance of diaphragm ultrasound thresholds to detect extubation failure at day 7

	Exdi < 10mm (right)	Exdi <10mm (left)	Exdi <10mm (right or left)	TFdi <30 (right)	TFdi <30 (left)	TFdi <30 (right or left)
Sensitivity	0,42	0,27	0,52	0,60	0,54	0,68
Specificity	0,68	0,72	0,54	0,37	0,41	0,29
Positive predictive value	0,22	0,18	0,19	0,17	0,16	0,16
Negative predictive value	0,85	0,81	0,84	0,80	0,80	0,81
Positive likelihood ratio	1,3	1,0	1,1	1,0	0,9	1,0
Negative likelihood ratio	0,9	1,0	0,9	1,1	1,1	1,1

Exdi, Diaphragm excursion; TFdi, Thickening fraction of diaphragm

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e-Table 2. Comparison of patients who developed acute respiratory failure within the 48h after extubation versus the others (n=191)

	Extubation success n=163 (85%)	Acute respiratory failure at h48 n=28 (15%)	p
Age, years	68 ± 14	67 ± 17	0.46
Male gender, n (%)	102 (63%)	19 (68%)	0.59
Body Mass Index, kg/m ²	28 ± 7	26 ± 5	0.40
SAPS II at admission, points	47 ± 18	53 ± 20	0.05
Duration of mechanical ventilation before Extubation, days	5 (2-10)	5 (2-10)	0.63
Risk factor for difficult weaning			
Age > 65 years, n (%)	105 (64%)	19 (68%)	0.72
Mechanical ventilation > 7 days, n (%)	66 (41%)	9 (32%)	0.40
Underlying chronic cardiac disease, n (%)	86 (53%)	9 (32%)	0.04
Chronic lung disease, n (%)	48 (29%)	7 (25%)	0.63
Clinical assessment			
MRC score, points	45 ± 14	40 ± 17	0.01
MRC < 48, n (%)	73/152 (48%)	16/26 (62%)	0.20
Cervical hypotonia, n (%)	10/153 (7%)	3/26 (12%)	0.36
Abundant sputum, n (%)	27/152 (18%)	6/27 (22%)	0.58
Cough strength			<0.01
Ineffective (0-1), n (%)	6/154 (4%)	7/27 (26%)	
Moderate (2-3), n (%)	87/154 (57%)	14/27 (52%)	
Effective (4), n (%)	61/154 (40%)	6/27 (22%)	
Spirometric measurements			
Respiratory Rate, min ⁻¹	27 ± 7	28 ± 10	0.71
Tidal Volume, mL	367 ± 130	388 ± 113	0.76
Vital Capacity, mL	1140 ± 516	943 ± 503	0.19
Maximal inspiratory pressure, cm H ₂ O	-42 ± 16	-43 ± 19	0.94
Maximal expiratory pressure, cm H ₂ O	51 ± 24	48 ± 25	0.94
Cough peak expiratory flow, L/min	61 ± 24	59 ± 23	0.32
CPEF ≤ 35, n (%)	13/137 (10%)	1/23 (4%)	0.42
CPEF ≤ 60, n (%)	78/137 (57%)	15/23 (61%)	0.72
Rapid shallow breathing index, breaths/min/ml	84 ± 46	74 ± 32	0.98
f/V _T > 105, n (%)	36/119 (30%)	6/21 (29%)	0.88
Ultrasonographic measurements			
Diaphragm excursion			
right, mm	13 ± 7	11 ± 8	0.13
right E < 10, n (%)	53/161 (33%)	11/28 (39%)	0.51
left, mm	14 ± 7	14 ± 6	0.66
left E < 10, n (%)	36/135 (27%)	8/25 (32%)	0.58
Diaphragm thickness			
right, mm	2.6 ± 1.1	2.6 ± 0.9	0.35
left, mm	2.5 ± 1.0	2.4 ± 1.0	0.69
Diaphragm thickening			
right, (%)	28 ± 25	44 ± 57	0.83
right Tfdi < 30, n (%)	90/139 (65%)	13/26 (50%)	0.15
left, (%)	31 ± 34	51 ± 64	0.27
left Tfdi < 30, n (%)	74/124 (60%)	11/22 (50%)	0.40

Continuous variables are expressed as mean ± standard deviation or median (interquartile range) and categorical variables are expressed as absolute value (%). SAPS II, Simplified Acute Physiology Score; NIV, Noninvasive ventilation; MRC score, Medical research council score; CS, Cough strength; CPEF, Cough peak expiratory flow; Exdi, Excursion of the diaphragm; Tfdi, Thickening fraction of the diaphragm

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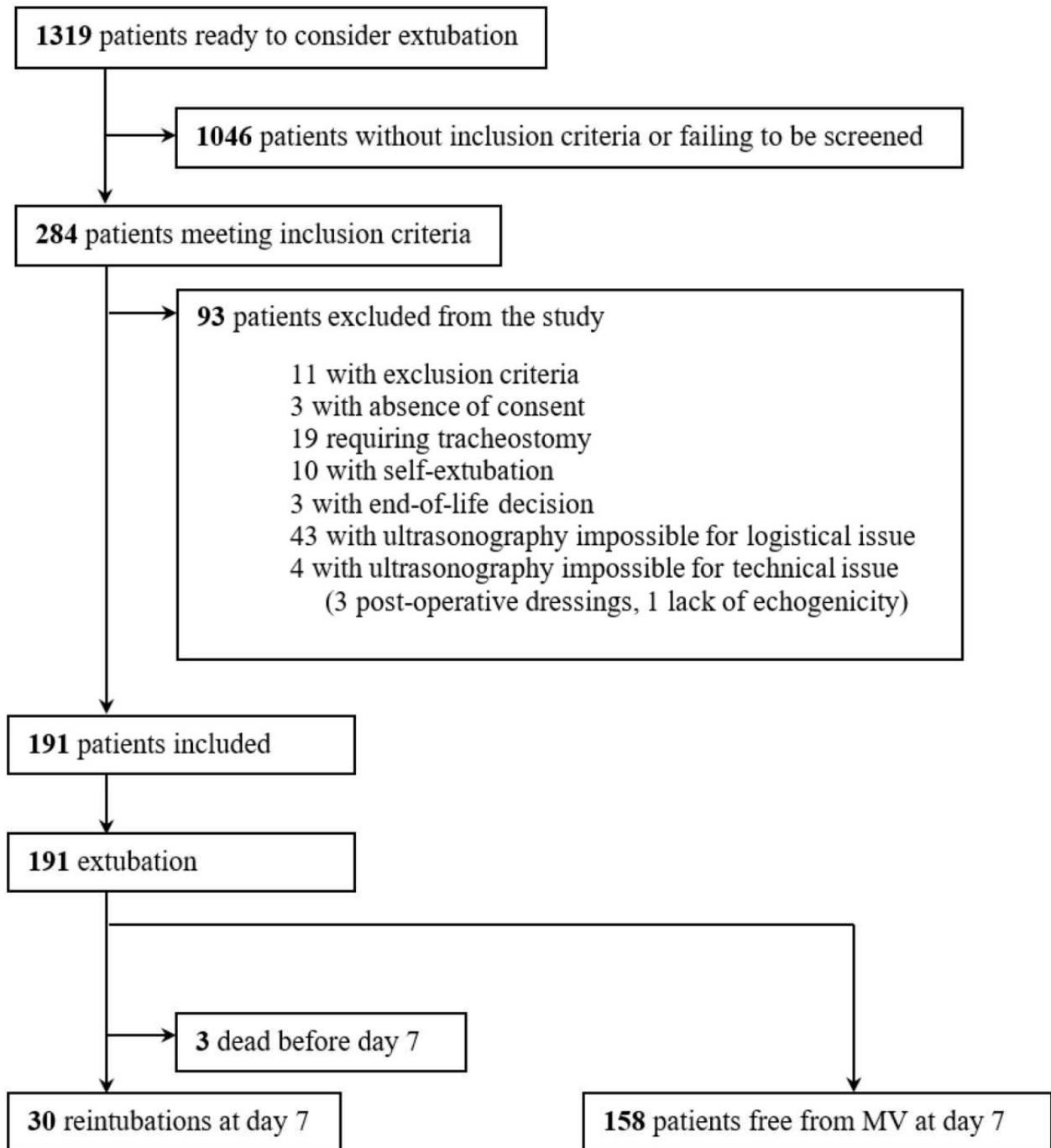
e-Table 3. Impact exposure variables on extubation outcome at day 7

Variables	Event	Univariate analysis		Multivariate analysis			
			P value	B	OR	95% CI	P value
SAPS II at admission, <i>points</i>	Extubation success	46 ± 18	0.01	0.022	1.02	1.00 -1.05	0.05
	Failure at day 7	55 ± 18					
Underlying chronic cardiac disease, <i>n (%)</i>	Extubation success	84 (53%)	0.04	-0.721	0.49	0.21-1.15	0.1
	Failure at day 7	11 (33%)					
MRC score, <i>points</i>	Extubation success	46 ± 14	<0.01	-0.018	0.98	0.96 - 1.01	0.19
	Failure at day 7	38 ± 15					
Cough strength			<0.01	-1.030	0.36	0.17 - 0.74	<0.01
Ineffective, <i>n (%)</i>	Extubation success	7/148 (5%)					
	Failure at day 7	6/33 (18%)					
Moderate, <i>n (%)</i>	Extubation success	79/148 (53%)					
	Failure at day 7	22/33 (67%)					
Effective, <i>n (%)</i>	Extubation success	62/148 (42%)					
	Failure at day 7	5/33 (15%)					

SAPS II, Simplified Acute Physiology Score; MRC score, Medical Research Council score; OR, Odds

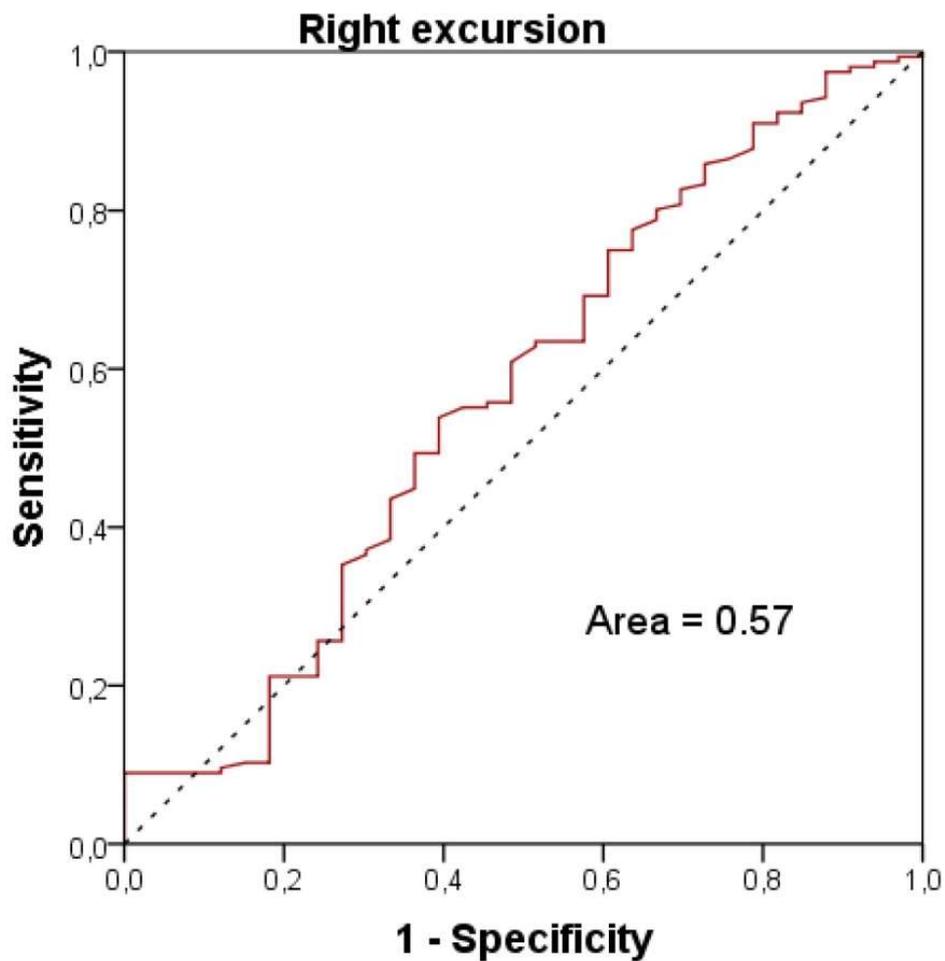
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e-Figure 1. Flow chart of the study



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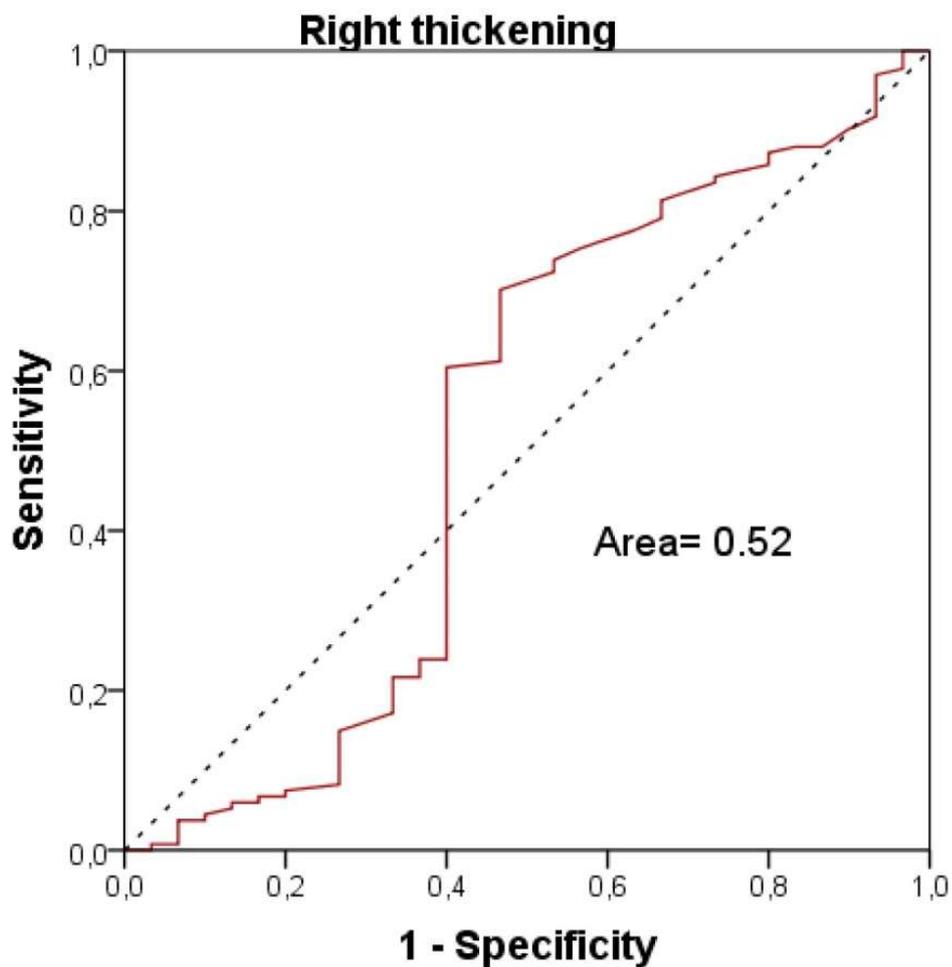
e-Figure 2. Receiver operating characteristic (ROC) curves for right excursion.



The area under the curve is expressed as a ratio of the total area.

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e-Figure 3. Receiver operating characteristic (ROC) curves for right thickening.



The area under the curve is expressed as a ratio of the total area.

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Travail n°4

*Diagnostic accuracy of diaphragm ultrasound in detecting and
characterizing patient-ventilator asynchronies during non-invasive
ventilation*

(Under submission)

1. ARTICLE TITLE:

Diagnostic accuracy of diaphragm ultrasound in detecting and characterizing patient-ventilator asynchronies during non-invasive ventilation.

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ABSTRACT (297 words)

Background: Management of acute respiratory failure by noninvasive ventilation (NIV) is often associated with asynchronies, like auto-triggering or delayed cycling, incurred by leaks from the interface. These events are likely to impair patient's tolerance and to compromise NIV. The development of methods for easy detection and monitoring of asynchronies is therefore necessary. We describe two new methods to detect patient-ventilator asynchronies, based on ultrasound analysis of diaphragm excursion or thickening combined with airway pressure. We tested these methods in a diagnostic accuracy study.

Methods: Fifteen healthy subjects were placed under NIV and subjected to artificially-induced leaks in order to generate the main asynchronies (auto triggering or delayed cycling) at event-appropriate times of the respiratory cycle. Asynchronies were identified and characterized by combined analysis of ultrasound records and airway pressure waveform, both were visualized on the ultrasound screen. The performance and accuracy of diaphragm excursion and thickening to detect each asynchrony were compared with a "control method" of flow/pressure tracings alone, and a "working standard method" combining flow, airway pressure, and diaphragm electromyography signals analyses.

Results: Ultrasound recordings were performed for the 15 volunteers, unlike electromyography recordings which could be collected in only 9/15 patients (60%). Auto-triggering was correctly identified by continuous recording of electromyography, excursion, thickening, and flow/pressure tracings with sensitivity of 93%[95%CI:89-97], 94%[95%CI:91-98], 91%[95%CI:87-96], and 79%[95%CI:75-84], respectively. Delayed cycling was detected by electromyography, excursion, thickening, and flow/pressure tracings with sensitivity of 84%[95%CI:77-90], 86%[95%CI:80-93], 89%[95%CI:83-94], and 67%[95%CI:61-73] respectively.

Conclusion: Ultrasound is a simple, bedside adjustable, clinical tool to detect the majority of patient-ventilator asynchronies associated with NIV leaks, provided that it is possible to visualize the airway pressure curve on the ultrasound machine screen. Ultrasound detection of auto-triggering and delayed cycling is more accurate than isolated observation of pressure and flow tracings, and more feasible than electromyogram.

Introduction

Noninvasive ventilation (NIV) is one of the main management tools of acute respiratory failure.(1) Its usefulness is often compromised by patient's discomfort or refusal(2) brought about by asynchronies.(3,4) The unavoidable leaks around the mask interfere with the ventilator performance and generate desynchronization between the respiratory demands pattern of the patient and the ventilator pressurizations.(5) Expiratory leaks can erroneously be detected by the ventilator as inspiratory effort, leading to auto-triggering (AT),(3) alike, inspiratory leaks can be interpreted as sustained inspiration, leading to delayed cycling (DC).(3) AT is defined as a cycle delivered by the ventilator without a prior inspiratory demand of the patient.(4) DC is a cycle with mechanical inspiratory time of more than 2-fold the patient inspiratory time.(4) The recognition and monitoring of these asynchronies are of clinical importance as they could be a major determinant of patient's tolerance, a cornerstone of successful NIV that could spare patient intubation.(2) Recent studies showed that the incidence of asynchronies during NIV amount to 40%,(4) which remains high despite implementation of algorithm with air leak detection and compensation.(3,6,7) The concurrent inspection of airway and flow tracings on the ventilator screen is not sensitive enough, even with training or expertise,(6) hence the need to monitor inspiratory effort in order to detect asynchronies during NIV.(6) Surface diaphragm electromyography (EMGdi) is the current reference technique, though not always effective and cannot be routinely used at bedside.(3,4,7)

Patient's inspiratory effort under NIV can be assessed using diaphragm ultrasound (USdi).(8) Monitoring the diaphragm dome excursion or its muscle thickening in the apposition zone, in time-motion (TM) mode, helps detect the start and end of diaphragm contraction.(9) If coupled with airway pressure monitoring, USdi could theoretically help identify major asynchronies incurred by NIV leaks. We conducted this study on healthy volunteers. Its

objective was to determine if USdi could improve the detection of main ventilator asynchronies in comparison with pressure and flow tracings. We hypothesized that this technique could be as accurate as EMGdi, the current reference technique.

Methods

This study was designed and centered at *Henri Mondor* University Hospital, approved by the French ethics Committee *CPP Ile-de-France VIII*, and was registered (number NCT03114384) online on clinicalTrials.gov. Subjects were included in the study if they were healthy, with no respiratory comorbidity, and aged more than 18 years. Pregnancy, lack of social care, and legal immaturity were the exclusion criteria. Each study participant was directly recruited after having provided a written informed consent.

Experimental design and sequence of interventions

Healthy volunteers were subjected to a 45-minute noninvasive ventilation (NIV) session. NIV was administered via an oronasal mask mounted on an intensive care unit (ICU) ventilator (Engstrom Carestation, GE Healthcare). The NIV algorithm was intentionally turned off in order to allow leaking and generate planned subject-ventilator asynchronies. In an attempt to reproduce the most common asynchronies occurring under NIV, a T-piece plug was inserted on the inspiratory limb of the ventilator circuit (**Figure 1**). A plug-opening/closing sequential series reproduced the main asynchronous leaks, depending on the time of the event as follows: auto-triggering (AT) if the plug was manually opened during expiration, and delayed cycling (DC) if the plug was manually opened at the end of inspiration. The investigator and the ventilator were both positioned behind the participant receiving NIV in a way that the latter cannot see the manipulations performed on the T-piece. Each leak was reported in real time by a time mark on the data acquisition software, Acqknowledge 4.0. These marks were used in association with flow/pressure tracings for the subsequent identification of asynchronies by the reference standard method.

Before recording, each subject was equipped with an EMG recording device and an ultrasound probe was fixed using a shape memory arm. A preliminary 15-minute NIV

sequence was run to accustom the participant to the interface and to test whether the leaks could induce the desired asynchrony. Given that it was impossible to simultaneously record excursion and thickening, each subject underwent two successive series of AT and DC asynchronies to separately assess the continuous monitoring of diaphragmatic excursion and then diaphragmatic thickening. The aim was to generate an asynchrony at random about a dozen times per session and per asynchrony type. The time interval between each asynchrony and the following was about 10 seconds, the total duration of each recording was 5-10 minutes.

Monitoring of flow rate, airway pressure and diaphragm electromyography

Airway flow was recorded using a heated pneumotachograph RX137G (Biopac Systems, Goleta, CA, USA) inserted between the mask and the Y-piece of the ventilator circuit and connected to a differential pressure transducer TSD160A (Biopac Systems, Goleta, CA, USA). Airway pressure was measured with a differential pressure transducer TSD160D (Biopac systems, Goleta, CA, USA) inserted between the mask and the pneumotachograph. The signals were obtained online using an analog-to-digital converter (MP 150, Biopac systems, Goleta, CA, USA) sampled at 1000Hz, and stored on a laptop for subsequent analysis with Acqknowledge 4.0 software.

The diaphragm electromyography (EMG_{di}) was recorded with two surface electrodes placed bilaterally on the floating ribs, and a reference electrode placed on the sternum. Neck muscles electromyogram was recorded with two surface electrodes placed on the posterior neck triangle (to record scalene EMG activity) or on the sternocleidomastoid muscle (to record sternocleidomastoid EMG activity), with a reference electrode placed on the sternum. EMG signals were recorded using a BioNomadix module (Biopac systems, Goleta, CA, USA) and then stored on a laptop for subsequent analysis (Acqknowledge 4.0, Biopac Systems, Goleta, CA, USA).

Ultrasound recordings

The airway pressure curve was displayed on the ultrasound screen using a barometric pressure gauge (Fujikura, Sensor type: XFMP-050KPGP3) connected to an analog converter. This device allowed implementing pressure signal on the screen as a time-dependent curve which was coupled with ultrasound images. Ultrasound recordings of diaphragmatic excursion and thickening were performed using an ultrasound machine (Vivid S5, General Electric Healthcare) with either high definition probe (12 MHz) for thickening of the apposition zone or a high penetration probe (4 MHz) for the excursion of the dome. Images were acquired on a laptop with a video capture device (Startech.com USB 3.0 HD Video Capture Device - 1080p) and recorded over a period of 10 minutes. An articulated, shape-memory arm held the ultrasound probe in the same position during the entire recording session. The diaphragm was located via the right subcostal route for the excursion or via the right anterior axillary line for the thickening, as previously described. Diaphragmatic thickening and excursion were recorded in time-motion (TM) mode. Scrolling speed was set as slow as possible to get a minimum of three cycles on the same image. Ultrasound video loops were recorded and stored for subsequent offline analysis.

Analysis of the events

Asynchronies were analyzed cycle by cycle with four different approaches:

1. “Reference standard method” used the marked events and the flow/pressure tracings to detect and characterize each asynchrony. If the ventilator cycle was delivered immediately after an expiratory leak, the event was classified as AT. If the inspiratory time was prolonged by an inspiratory leak, the event was DC.
2. “Working standard method” used EMGdi with flow/pressure tracings, irrespective of the marked events. This analysis was restricted to patients in whom a sufficient-quality signal helped determine the start and end of the inspiratory effort. AT was a ventilator cycle

delivered in the absence of EMGdi activity. DC was deemed present if the pressurization continued beyond the cessation of EMGdi activity.

3. “USdi method” used ultrasound video loops with airway pressure tracings, irrespective of the marked events. Variations of diaphragm thickness and its excursion were used to detect each inspiratory effort. AT was a ventilator cycle delivered in the absence of diaphragmatic displacement or thickening. DC was flagged if the pressurization continued beyond the end of diaphragmatic excursion or thickening.
4. “Control method” used the flow/pressure tracings alone, without the marked events. AT was suspected if the insufflation appeared premature, shortened, or altered. DC was considered in long insufflations with prolonged pressurization and irregular concurrent flow.

Statistics

The diagnostic accuracy of the working standard method, the USdi method using excursion, the USdi method using thickening, and the control method were assessed versus the reference standard method. Each ventilatory cycle was evaluated as true positive (TP), false positive (FP), true negative (TN), or false negative (FN). Detecting an asynchrony by the working standard method, the USdi method, or the control method was flagged TP if consistent with the reference standard method. The erroneous detection of an asynchrony was classified as FP. The lack of detection of an asynchrony was classified as FN. The correct diagnosis of a synchronous cycle was considered as TN. Standard formulas were used to calculate the sensitivity $[TP/(TP+FN)]$, specificity $[TN/(TN+FP)]$, accuracy $[(TP+TN)/(TP+TN+FP+FN)]$, likelihood ratio (LR) of positive test $[sensitivity/(1-specificity)]$, LR of negative test $[(1-sensitivity)/specificity]$, and Youden’s index (sensitivity + specificity - 1). Sensitivities and specificities were compared using the method advised by Newcombe et al.(10) A two-tailed testing was used by convention and p value <0.05 was considered as statistically significant.

The sample size was calculated based on the number of ventilatory cycles required to analyze, which was estimated at 101 given that the prevalence of asynchrony is about 30% of breathing cycles, with an expected sensitivity of 90% for the USdi method and a marginal error of 7%. By estimating that each type of asynchronies should be randomly generated at least 12 times per participant, with an average interval of about 10 seconds, it was planned to include about 15 adults over the study period.

Continuous variables are expressed in median [Interquartiles: 25th and 75th percentiles]. Statistical analyses were performed using SPSS software (version 16.0, SPS Inc, Chicago, Illinois). No outliers were detected in the analyses, and the data presented here are comprehensive.

Results

The 15 participants' baseline characteristics are listed in **table 1**. A total of 1,925 cycles were recorded and were all included in the analysis. The experimental setup made it possible to observe 962 respiratory cycles during USdi excursion recordings and 963 cycles during USdi thickening recordings. Interestingly, each leak yielded its expected event. Of the whole 1,925 analyzed cycles, 537 (28%) asynchronies were identified by the reference standard method as AT (n=312, 16%) and DC (n=225, 12%). All subjects exhibited a consistent incidence of AT and DC (Table S1).

The control method enabled the detection of AT and DC with sensitivities of 79% [95%CI: 75-84] and 67% [95%CI: 61-73], and specificities of 98% [95%CI: 97-99] and 96% [95%CI: 96-97], respectively (**Table 2**). EMG method had a sufficient quality signal to discern the start and end of the inspiratory effort in only nine participants (60%), allowing the analysis of 995 of the 1,925 recorded respiratory cycles. It enabled the detection of AT and DC with sensitivities of 93% [95%CI: 89-97] and 84% [95%CI: 77-90], and specificities of 98% [95%CI: 97-99] and 99% [95%CI: 98-100], respectively. USdi was possible in all 15 subjects in whom asynchronies were detected at sensitivities above 90 and 85%, and specificities above 97 and 98%, for AT and DC, respectively (**Table 2, Figure 2, Video 1 and 2**). Overall, USdi and the working standard method had similar sensitivities and specificities which were statistically significantly higher than those of the control method (**Table 2, Table S2 and Table S3**) when compared as proposed by Newcombe et al.(10)

Discussion

We herein describe a technique relying on combined analyses of USdi signals and airway pressure waveform displayed on the ultrasound screen to detect the main asynchronies occurring during NIV in healthy volunteers. This method was definitively more sensitive than isolated analysis of flow and pressure waveform, and had better feasibility than EMGdi.

Asynchrony detection

Detection and mitigation of asynchronies in ventilated patients remain a great challenge for intensivists since mismatch between ventilator pressurization and patient's demand has been recognized as an outstanding clinical issue for years.(11,12) In terms of pathophysiology, the main underlying mechanisms of asynchronies differ significantly between invasive and noninvasive ventilation. In patients under invasive mechanical ventilation, ineffective triggering is the most common asynchrony during pressure support (12–14) and its occurrence is vastly enhanced by overassistance.(12,15–18) During assist-control ventilation, premature cycling and double triggering often occur as a consequence of the low insufflation time.(12,19) Asynchronies are common in invasively ventilated patients(12,13) and associated with bad prognosis, including discomfort, sleep disorders,(20) increased need for sedatives,(21) prolonged mechanical ventilation,(12,14) and higher ICU and hospital mortality,(13) although a causal relationship cannot be established.

In patients under NIV, asynchronies have also been reported albeit with a higher incidence than with invasive mechanical ventilation (up to 40-50% of patients),(4) mostly in the form of AT (20%) and DC (23%), and are mainly incurred by leaks present around the mask.(3,4) These asynchronies interfere with patient's tolerance, which may compromise NIV efficiency and feasibility.(2) Although the role of asynchronies in precipitating NIV failure has not been

demonstrated to date, robust and simple methods to detect and reduce their incidence are required.(6)

A new method

The detection method we herein describe is robust, simple and could be an interesting alternative to the usual methods used in clinical settings to detect asynchronies. The simple analysis of flow and pressure waveform (named “control method” in our study) could be easily conducted but its accuracy is questioned due to its poor sensitivity as previously documented.(6,22) On the other hand, a rigorous analysis comparing EMGdi signal and flow/pressure tracings (named “working standard method” in our study) has a much better diagnostic value(3,4,7) but poor feasibility because it is difficult to get a stable electrical signal. From a physiological point of view, excursion and thickening are not equivalent. The diaphragm displacement could be passively induced by pressurization of the ventilator, whereas diaphragm thickening can more reliably depict an active muscle contraction.(8) However, their performance seemed to be equivalent for the detection of asynchronies in the present study. Our results encourage the innovative use of USdi to detect, characterize, and quantify asynchrony under NIV at the bedside in intensive care units (ICU). Future studies in patients under invasive and non-invasive ventilation are needed to validate the technique. We also hope that the technological development of ultrasound devices will make USdi assessment even more reliable over time.(23)

Limits

The clinical application should however be counterbalanced by some limitations. First, we generated replicable and characteristic asynchronies, occurring at fairly regular intervals, thus relatively easy to detect and classify. Second, the experimental design reproduced only the most frequent asynchronies occurring during NIV and related to mask leaks (AT and DC).

Future studies should evaluate the usefulness of USdi in detecting and characterizing others typical asynchronies, though less common but are much more difficult to experimentally induce. Of the latter, three are clinically meaningful: i) ineffective triggering happens when an inspiratory effort is not met with inspiratory pressurization, and could reflect dynamic hyperinflation; ii) premature cycling is a cycle with mechanical insufflation shorter than the patient's inspiratory time and often occurs in the presence of restrictive respiratory mechanics;⁴ iii) double or reverse triggering is defined as two cycles separated by very short expiratory time and could be related to an insufficient level of assistance.¹² Third, our work needs to be conducted on ICU patients. Our healthy participants were young and slender, with good echogenicity and cooperation allowing a good stability of USdi signal. They also had a quite slow respiratory rate (which may not be the case for ICU dyspneic patient) and big tidal volumes which probably augmented the diaphragmatic excursion(24) and facilitated the detection of inspiratory efforts with USdi. A wider use of this method in patients could be hindered by the vast variability of respiratory profiles, instability of the ultrasound signal, and the expected poor tolerance of patients. Last, the study design required an “a posteriori analysis” of curves and video recordings. An online analysis should be considered for future developments.

In conclusion, USdi accurately detected asynchronies during NIV in healthy volunteers. This technique is promising and should be evaluated in clinical settings, and compared with emerging automated techniques based on EMGdi signal or respiratory flow signal.(25)

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FIGURE LEGENDS

Figure 1 Experimental setup

The ventilator was positioned behind the healthy participant. A T-piece was inserted on the inspiratory limb of the ventilator (Fig 1A, in red) and was suddenly opened to generate specific asynchronies linked to the precise timing of the leaks: auto-triggering during expiration (Fig 1B) or prolonged insufflation during inspiration (Fig 1C). Schematic patterns of concomitant diaphragm electromyogram (EMGdi), airway pressure (Paw), and respiratory flow (Q°) tracings are displayed on the left for each asynchrony.

Figure 2 Auto-triggering and delayed cycling detected by monitoring of diaphragmatic excursion or thickening in TM mode.

Diaphragmatic dome movement (1A and 1B) and diaphragm cyclic thickening (1C and 1D) help detect the different respiratory phases.

The diaphragmatic dome moves closer to the probe (upwards) during inspiration (I) and moves away from it during expiration (E). An auto-triggered cycle caused by the ventilator is defined as a pressurization that is not associated with any excursion of the diaphragm (1A). Prolonged insufflation is characterized by a prolonged ventilator pressurization, far beyond the end of diaphragm excursion (1B).

The diaphragm thickens in inspiration (I) and thins out in expiration (E). An auto-triggered cycle initiated by the respirator is recognized as pressurization that is not associated with any diaphragm thickening (1C). Prolonged insufflation is characterized by a respirator pressurization prolonged far beyond the end of diaphragm thickening (1D).

Table 1. Characteristics of the participants (n = 15)

Age, years	30 [28-33]
Male, n (%)	9 (60%)
BMI, kg.m ⁻²	23 [21-25]
<i>Respiratory</i>	
SpO ₂ , %	99 [97-100]
RR, min ⁻¹	15 [11-16]
V _T , ml	800 [665-939]
Leaks rate, %	24 [7-38]
<i>Hemodynamic</i>	
HR, min ⁻¹	63 [56-73]
SBP, mmHg	111 [110-124]
DBP, mmHg	69 [61-76]
<i>Diaphragm ultrasound</i>	
Exdi, mm	22 [18-28]
End expiratory thickness, mm	3.2 [2-4.3]
TFdi, %	21 [14-39]

BMI, Body Mass Index; SpO₂, peripheral oxygen saturation; RR, respiratory rate; VT, tidal volume; HR, heart rate; SBP, systolic blood pressure; DBP diastolic blood pressure; Exdi, diaphragm excursion; TFdi, diaphragm thickening; Continuous variables are expressed in median [IQR]. Categorical variables are expressed in absolute value (%).

Table 2. Performance of diaphragm ultrasound and electromyogram to detect auto triggering (AT) and delayed cycling (DC), in comparison with airway pressure and flow waveform observation alone.

Asynchrony detection	Control method (Pressure and flow tracings observation alone) (n=1,925 cycles)	Working standard method (Pressure and flow tracings coupled with EMG) (n=995 cycles)	Diaphragm ultrasound method (Pressure waveform coupled with ultrasound)	
			Excursion (n=962 cycles)	Thickening (n=963 cycles)
Auto Triggering				
Sensitivity (%)	79	93	94	91
Specificity (%)	98	98	98	98
PPV (%)	89	91	91	91
NPV (%)	96	99	99	98
LR of positive test	40	51.3	50.4	53
LR of negative test	0.21	0.07	0.06	0.09
Diagnostic accuracy (%)	95	97	98	97
Youden's index	0.77	0.91	0.93	0.90
Delayed Cycling				
Sensitivity (%)	67	84	86	89
Specificity (%)	96	99	99	99
PPV (%)	72	92	90	93
NPV (%)	96	98	98	98
LR of positive test	19	81	66.9	94
LR of negative test	0.34	0.16	0.14	0.11
Diagnostic accuracy (%)	93	97	97	98
Youden's index	0.64	0.83	0.85	0.88
Any asynchrony				
Sensitivity (%)	75	89*	91*	90*
Specificity (%)	93	97*	96*	97*
PPV (%)	81	91	90	92
NPV (%)	91	96	97	96
LR of positive test	11.5	26.2	24.2	28.6
LR of negative test	0.27	0.11	0.09	0.10
Diagnostic accuracy (%)	89	94	95	95
Youden's index	0.69	0.86	0.87	0.87

*TM, Time mode; PPV, positive predictive value; NPV, negative predictive value, LR, likelihood ratio; * p value < 0.05 for differences in sensitivity or specificity to detect any asynchrony as compared with the control method.*

Figure 1. Experimental setup

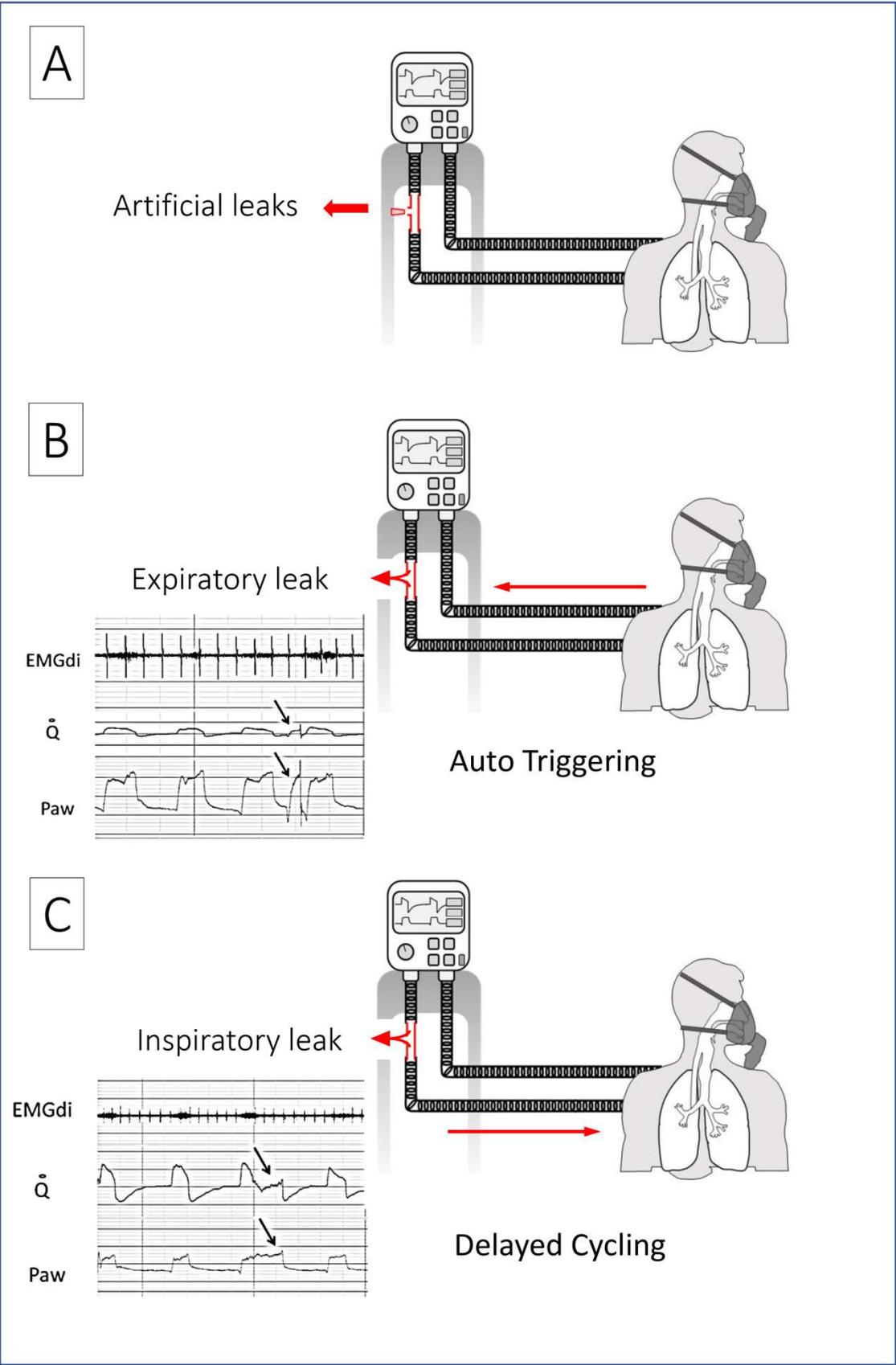


Figure 2. Auto-triggering and delayed cycling detected by monitoring of diaphragmatic excursion or thickening in TM mode

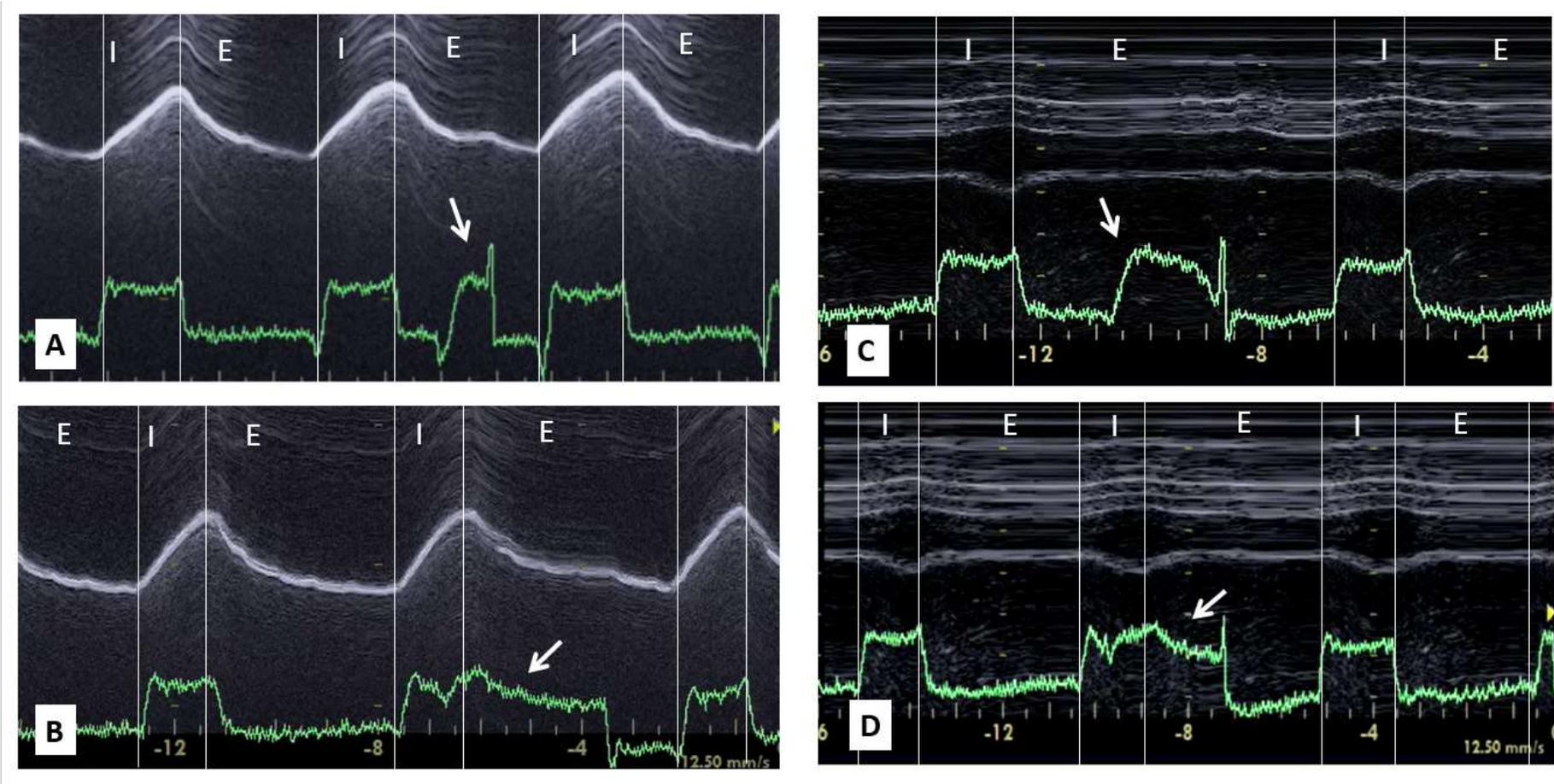


Table S1. Incidence of auto-triggering and delayed cycling for each subject

Subject	RR (min^{-1})	Cycles (n)	AT ($n, \%$)	DC ($n, \%$)
1	10	108	20 (19%)	18 (17%)
2	12	111	20 (18%)	17 (15%)
3	10	93	22 (24%)	15 (16%)
4	16	137	24 (18%)	15 (11%)
5	19	177	37 (21%)	15 (8%)
6	15	145	30 (21%)	17 (12%)
7	11	93	19 (20%)	9 (10%)
8	18	156	30 (19%)	22 (14%)
9	17	154	16 (10%)	14 (9%)
10	16	146	15 (10%)	8 (5%)
11	15	129	16 (12%)	14 (11%)
12	10	96	11 (11%)	12 (13%)
13	15	146	16 (11%)	15 (10%)
14	9	89	13 (15%)	11 (12%)
15	17	145	23 (16%)	23 (16%)

RR, Respiratory Rate; AT, Auto Triggering; DC, Delayed Cycling.

Table S2. Confusion Matrix for Auto-Triggering detection

		Reference		
		Positive	Negative	
Working standard Method (EMG)	Positive	154 <i>True Positive</i>	15 <i>False Positive</i>	n= 995 cycles
	Negative	12 <i>False Negative</i>	814 <i>True Negative</i>	
USdi Method (Excursion)	Positive	152 <i>True Positive</i>	15 <i>False Positive</i>	n= 962 cycles
	Negative	9 <i>False Negative</i>	786 <i>True Negative</i>	
USdi Method (Thickening)	Positive	138 <i>True Positive</i>	14 <i>False Positive</i>	n=963 cycles
	Negative	13 <i>False Negative</i>	798 <i>True Negative</i>	
Control Method (Flow /Pressure)	Positive	247 <i>True Positive</i>	32 <i>False Positive</i>	n= 1,925 cycles
	Negative	65 <i>False Negative</i>	1581 <i>True Negative</i>	

Table S3. Confusion Matrix for Delayed Cycling detection

		Reference		
		Positive	Negative	
Working standard Method (EMG)	Positive	103 <i>True Positive</i>	9 <i>False Positive</i>	n= 995 cycles
	Negative	20 <i>False Negative</i>	863 <i>True Negative</i>	
USdi Method (Excursion)	Positive	95 <i>True Positive</i>	11 <i>False Positive</i>	n= 962 cycles
	Negative	15 <i>False Negative</i>	841 <i>True Negative</i>	
USdi Method (Thickening)	Positive	102 <i>True Positive</i>	8 <i>False Positive</i>	n=963 cycles
	Negative	13 <i>False Negative</i>	840 <i>True Negative</i>	
Control Method (Flow / Pressure)	Positive	151 <i>True Positive</i>	60 <i>False Positive</i>	n= 1,925 cycles
	Negative	74 <i>False Negative</i>	1640 <i>True Negative</i>	

IV. Discussion et perspectives

Au total, ce travail de thèse a confirmé que l'échographie permettait d'évaluer l'atrophie du diaphragme en réanimation. L'appréciation du travail respiratoire par la fraction d'épaississement doit tenir compte des nombreuses limites de cet indice. L'échographie du diaphragme semble insuffisante pour orienter la décision d'extubation en réanimation mais pourrait être pertinente pour dépister et caractériser les principales asynchronies patient-ventilateur sous ventilation non-invasive. L'ensemble de nos résultats permet de renforcer l'intérêt de l'échographie du diaphragme en réanimation, tout en incitant à une certaine prudence concernant sa validité interne, son interprétation et ses implications cliniques.

Validité interne

La validité interne des indices actuels d'échographie diaphragmatique semble perfectible. Cette limite tient principalement à la variabilité dans l'acquisition des images. Malgré le perfectionnement des techniques échographiques, les grandeurs observées sont extrêmement petites, en particulier l'épaisseur de l'apposition dont la variation s'exprime en dixièmes de millimètres. La première étude de la thèse confirme que la fraction d'épaississement est un indice d'interprétation délicate. En effet, si la corrélation entre fraction d'épaississement et travail respiratoire observée en VNI a bien été confirmée en ventilation mécanique (164), une importante limitation de la technique provient de sa variabilité. Les variations de position ou d'angulation de la sonde expliquent probablement une grande partie des limites de l'échographie conventionnelle dans ce contexte. Il semble nécessaire de standardiser précisément le lieu de recueil de cet indice sur la zone d'apposition. En cas de suivi longitudinal des patients, il semble aussi indispensable d'avoir un repère cutané afin de réaliser la mesure toujours au même endroit.

Les techniques de Doppler tissulaire ou speckle tracking (2D strain) pourraient rendre l'évaluation de l'épaississement plus robuste (161,162). Ces deux techniques échographiques

permettent en effet d'améliorer l'enregistrement de la déformation tissulaire. Le suivi automatisé du déplacement spatial de marqueurs acoustiques endocardiques a ainsi permis d'obtenir une analyse fine de la déformation du tissu myocardique dans les différents axes de l'espace (longitudinal, radial et circonférentiel) (165). Cette technique est aujourd'hui aisément accessible en routine clinique échocardiographique (166). Son application au muscle diaphragmatique pourrait permettre de réduire sensiblement la variabilité de mesure et surtout d'intégrer des mouvements de déformation dans plusieurs dimensions. En effet, le diaphragme au niveau de la zone d'apposition présente un double mouvement d'épaississement et de translation. Ce double mouvement pourrait être à l'origine d'un biais de recueil important lors de l'analyse de l'épaississement.

Interprétation

L'autre limite importante tient à la variabilité adaptative permanente du système musculaire respiratoire. Notre travail montre ainsi que ces indices doivent être interprétés en fonction du terrain du patient, de la sédation et des conditions de charge respiratoire. Cette limite rend toute évaluation sans stimulation standardisée extrêmement difficile à interpréter, en dehors de situations caricaturales. La paralysie d'une coupole diaphragmatique est un diagnostic facile en ventilation spontanée : la coupole ne se déplace pas de façon synchrone (excursion nulle ou ascension inspiratoire paradoxale) et ne s'épaissit pas (épaississement nul ou amincissement inspiratoire paradoxal). Elle est d'autant plus facile à repérer qu'il s'y associe souvent un renforcement compensatoire du mouvement et/ou de l'épaississement de la coupole controlatérale. En revanche, le diagnostic échographique de dysfonction diaphragmatique uni- ou bilatérale est plus équivoque, comme en atteste la diversité des seuils proposés en réanimation : 10, 11 ou 25 mm pour l'excursion (140,141,167) ; 20, 29, 30 ou 34% pour l'épaississement (156,168–170).

Implications cliniques

Le deuxième travail de la thèse objective l'existence d'une atrophie diaphragmatique chez les patients de réanimation ventilés. Cette atrophie semble relativement spécifique du diaphragme et paraît favorisée par la présence d'un sepsis. Cette donnée est confirmée par de nombreuses autres études (111,151–153). Il est nécessaire de poursuivre ces travaux afin de :

- Mieux préciser les mécanismes à l'œuvre dans l'atrophie musculaire diaphragmatique et périphérique au cours des soins critiques. A ce titre, l'impact musculaire respectif des traitements par sédatifs (90,91), curares (94,95) et corticoïdes (93) mérite des travaux spécifiques complémentaires pour mieux définir, discriminer et comprendre les atteintes musculaires périphériques et respiratoires. L'utilisation de l'échographie musculaire répétée au même site après repérage semble pertinente pour comparer muscles respiratoires et muscles périphériques.
- Tester des stratégies thérapeutiques médicamenteuses et non médicamenteuses susceptibles d'amender cette atrophie. Certaines stratégies non médicamenteuses sont d'ores et déjà accessibles en réanimation et pourraient bénéficier d'une évaluation échographique répétée. La mobilisation précoce des patients ventilés en réanimation semble dénuée de risques majeurs (168,169) et paraît une stratégie naturelle pour limiter l'atrophie musculaire périphérique. L'entraînement plus spécifique des muscles respiratoires par application d'une charge résistive a également été proposée en réanimation (108,109) et pourrait aussi être évaluée par échographie.

Le troisième travail a répondu à une question clinique importante. Alors que des études préliminaires avaient laissé envisager que l'échographie du diaphragme puisse permettre de prédire le succès ou l'échec de l'extubation (141,170,171), il s'avère que ni l'altération de l'excursion, ni celle de l'épaississement du diaphragme n'est associée au risque de ré-intubation. Ce résultat est à confronter

aux multiples causes d'échec de l'extubation (172) : altération de la mécanique respiratoire sous-jacente (syndrome obstructif ou restrictif), insuffisance cardiaque systolique ou diastolique, défaut de clairance des sécrétions respiratoires, œdème de la filière laryngée et désordres neurologiques. La dysfonction neuro-musculaire diaphragmatique ne semble pas être un mécanisme prédominant de l'échec d'extubation dans une population générale de réanimation, une fois que l'épreuve de sevrage a été menée avec succès.

Perspectives

Le quatrième travail de la thèse ouvre un champ d'investigation. L'échographie pourrait un jour être utilisée pour détecter et reconnaître les asynchronies des patients ventilés en réanimation. Mais ce projet suppose de franchir plusieurs étapes ultérieures: validation chez le malade, validation en ventilation invasive et enregistrement sur une durée suffisante. Une évolution technologique est aussi nécessaire car l'affichage des courbes de pressions des voies aériennes sur l'échographe est loin d'être la règle en pratique clinique actuelle. Dans ce cadre, le développement récent de dispositifs ultrasoniques de détection automatisée des mouvements respiratoires est intéressant (173). On pourrait à terme imaginer une ventilation en boucle fermée basée sur le signal échographique du diaphragme. Deux types de boucles sont envisageables : une rétroaction immédiate basée sur l'épaississement cycle-à-cycle du diaphragme et une rétroaction retardée basée sur le niveau d'asynchronies. La rétroaction directe de l'assistance respiratoire pourrait être régulée et proportionnée à l'analyse automatisée de l'image de la contraction diaphragmatique au niveau de la zone d'apposition (sur le modèle de la NAVA-*Neurally adjusted ventilatory Assist* ou de la PAV-*Proportional assist ventilation*) (112,174). Une telle approche suppose toutefois d'automatiser le recueil de l'image échographique pour lui donner la forme d'un signal exploitable par le respirateur. Elles doit aussi tenir compte des pièges potentiels des boucles fermées dans le domaine de la ventilation : en NAVA par exemple, une commande neurale élevée sans rapport avec la mécanique respiratoire génère un risque d'amplification disproportionnée de la variabilité (175). Mais il est

également possible d'envisager une rétroaction retardée fondée sur l'analyse automatisée du nombre et du type d'asynchronies, pour évaluer en temps réel le niveau d'assistance optimal. Une prédominance d'effort inefficace pourrait traduire une sur-assistance, tandis que la présence de double-déclenchements ou de déclenchements inversés signerait une sous-assistance. Le positionnement de l'échographie par rapport aux techniques émergentes de détection automatisée des asynchronies à partir des courbes du respirateur mérite ainsi d'être évalué (176). Cette approche pourrait être intéressante en particulier en VNI.

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Résumé

Contexte Le diaphragme des patients de soins critiques subit une agression fréquente et précoce principalement en rapport avec la ventilation mécanique et le sepsis. Cette agression entraîne une dysfonction diaphragmatique souvent méconnue dans les premiers jours de réanimation car cliniquement silencieuse. Au moment de la levée de sédation, elle peut se révéler un facteur pronostic décisif sur la durée de sevrage ventilatoire, la durée de séjour et la survie. Des méthodes simples et robustes sont nécessaires pour mieux caractériser certaines propriétés du diaphragme des patients de réanimation : sa trophicité, sa puissance et son couplage à la ventilation mécanique. L'échographie est une technique simple et accessible qui permet l'observation superficielle et en profondeur de ce muscle respiratoire. **Objectifs** Comprendre et préciser la signification physiologique de différents indices échographiques utilisables par le clinicien pour aborder le diaphragme. Caractériser l'atrophie musculaire associée aux premiers jours de ventilation mécanique. Déterminer la pertinence de l'échographie du diaphragme dans différentes situations cliniques : aide à la décision d'extubation et dépistage des asynchronies patient-ventilateur. **Populations et Méthodes** Trois études cliniques prospectives descriptives (dont une multicentrique) et une étude chez le volontaire sain ont servi de support à la thèse. **Résultats** La fraction d'épaississement mesurée au niveau de la zone d'apposition du diaphragme semble corrélée au travail respiratoire chez des patients sous ventilation non invasive mais l'indice est influencé par de multiples facteurs et sa précision affaiblie par une variabilité élevée. Une atrophie du diaphragme pendant les cinq premiers jours de ventilation est visualisable par échographie de la zone d'apposition et ne semble pas corrélée à l'atrophie du pectoral. Ni l'excursion, ni l'épaississement mesurés après réussite d'une épreuve de ventilation spontanée et avant extubation ne peuvent aider à prédire l'issue de l'extubation. En revanche l'observation combinée des mouvements diaphragmatiques enregistrés en mode temps-mouvement couplés aux courbes de pression des voies aériennes permet le dépistage et la caractérisation des principales asynchronies en ventilation non invasive chez le volontaire sain. **Conclusion** L'échographie permet d'investiguer l'atrophie du diaphragme en réanimation. L'appréciation du travail respiratoire par la fraction d'épaississement doit tenir compte des nombreuses limites de cet indice. L'échographie du diaphragme semble peu judicieuse pour orienter la décision d'extubation en réanimation mais pourrait être pertinente pour dépister et caractériser les principales asynchronies patient-ventilateur sous ventilation non-invasive.

Summary

Background Patient diaphragms experience frequent and early aggression related to mechanical ventilation and sepsis in critical care. This aggression causes a diaphragmatic dysfunction which is often underestimated in the first days of ICU stay because it is clinically silent. It can however be a decisive prognostic factor associated with duration of weaning from mechanical ventilation, length of stay and mortality. Simple and robust methods are needed to better characterize some diaphragm properties in ICU: its trophicity, strength and coupling to mechanical ventilation. Ultrasound is a simple and accessible technique that allows superficial and deep observation of the diaphragm. **Objectives** Understand and clarify the physiological significance of the different ultrasound indices that can be used by the clinician to explore the diaphragm. Characterize the muscular atrophy associated with the first days of mechanical ventilation. Determine the relevance of diaphragm ultrasound in different clinical situations: support for the order-to-extubate decision and screening for patient-ventilator asynchronies. **Populations and Methods** Three descriptive prospective clinical studies (including one multicenter) and one study in healthy volunteers were used to support the thesis. **Results** Measurement of the thickening fraction of the diaphragm in zone of apposition appears to be correlated with work of breathing in patients under non-invasive ventilation, but the index is influenced by multiple factors and its precision weakened by a high variability. An atrophy of the diaphragm during the first five days of ventilation is noticeable by ultrasound in zone of apposition and does not seem to correlate with the atrophy of the pectoralis. Neither the excursion nor the thickening fraction measured after a successful spontaneous breathing test and before the extubation can help to predict its success. On the other hand, the combined analyze of diaphragmatic movements in time-motion mode and airway pressure curves makes it possible to diagnosis and characterize the main asynchronies in noninvasive ventilation in healthy volunteer. **Conclusion** Ultrasound enables the investigation of the diaphragm atrophy in ICU. The appreciation of the respiratory work of breathing by the thickening fraction of thickening must be tempered by the numerous limits of this index. The diaphragm ultrasound seems injudicious to guide the decision to extubate in ICU but could be relevant to detect and characterize the main patient-ventilator asynchronies under non-invasive ventilation.