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1 | SUPPORTING INFORMATION

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Association of diaphragm thickness and echogenicity with age, sex, and body mass index in healthy subjects

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Abstract

Introduction/Aims: Diaphragm ultrasound is increasingly used in the diagnosis of diaphragm dysfunction and to guide respiratory management in patients with neuromuscular disorders and those who are critically ill. However, the association between

Abbreviations: AIC, Akaike's information criterion; BMI, body mass index; ICC, Intraclass correlation coefficient; ICU, intensive care unit; NMD, neuromuscular disorder; $T_{end\text{-}exp}$, diaphragm thickness at resting end-expiration; $T_{max\text{-}insp}$, diaphragm thickness at maximal end-inspiration.

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diaphragm ultrasound variables and demographic factors like age, sex, and body mass index (BMI) are understudied. Such relationships are important for correct interpretation of normative values and comparison with selected patients groups. The aim of this study was to determine the associations between diaphragm ultrasound variables and subject characteristics.

Methods: B-mode ultrasound was used to image the diaphragm at the zone of apposition in 83 healthy subjects. Diaphragm thickness at resting end-expiration ($T_{end\text{-}exp}$), diaphragm thickness at maximal end-inspiration ($T_{max\text{-}insp}$), diaphragm thickening ratio ($T_{max\text{-}insp}/T_{end\text{-}exp}$), and diaphragm echogenicity were measured. Multivariate linear regression was used to explore the associations between diaphragm ultrasound variables and subject characteristics.

Results: $T_{end\text{-}exp}$, $T_{max\text{-}insp}$, and thickening ratio do not change with age whereas diaphragm echogenicity increases with age. The thickening ratio had a weak negative association with BMI, while $T_{end\text{-}exp}$ was positively associated with BMI. Men had a larger $T_{end\text{-}exp}$ and $T_{max\text{-}insp}$ than women ($T_{end\text{-}exp}$ 1.6 ± 0.5 and 1.4 ± 0.3 mm; $p = .011$, $T_{max\text{-}insp}$ 3.8 ± 1.0 and 3.2 ± 0.9 mm; $p = .004$), but similar thickening ratios.

Discussion: Diaphragm thickness, thickening, and echogenicity measured with ultrasound are associated with factors such as age, BMI, and sex. Therefore, subject characteristics should be considered when interpreting diaphragm ultrasound measurements. In the absence of normative values, matched control groups are a prerequisite for research and in clinical practice.

KEYWORDS
diaphragm, intensive care unit, neuromuscular disorders, normative values, ultrasound

1 | INTRODUCTION

Diaphragm weakness is a common feature in patients with neuromuscular disorders (NMDs) and those who are critically ill. In many NMDs, weakness of the diaphragm leads to dyspnea, sleep disturbances, and lung infections, and is a major contributor to death.[1] In critically ill patients, mechanical ventilation induces diaphragm injury and atrophy, leading to ventilator dependency and difficult weaning.[2] In both settings, reliable assessment of diaphragm function is to identify early signs of respiratory insufficiency, monitor disease progression, and guide individual respiratory management.

Ultrasound is increasingly used as tool to assess diaphragm function and structure in NMD patients and critically ill patients.[3,4] The costal diaphragm can be visualized at its insertion in the anterior thoracic wall, the so-called zone of apposition. The change in thickness from expiration to inspiration is used to quantify diaphragm function.[3,4] The assessment of the muscle ultrasound gray level, or echogenicity, reflects structural alterations in muscles due to, for example, fibrosis and inflammation.[5] Echogenicity analysis of skeletal muscles is a well-known and reliable tool for screening, diagnosing, and follow-up of NMDs.[5,6]

Thickness and echogenicity of peripheral muscles are dependent on subject characteristics such as age, body mass index (BMI), and sex.[7] However, it is unknown if diaphragm thickness and echogenicity also depend on these characteristics. Such relationships are important to identify those subject characteristics that should be taken into account when interpreting diaphragm ultrasound measurements in clinical practice or research. The aim of this study was to determine the association of diaphragm thickness and echogenicity with age, sex, and BMI using a standardized approach.

2 | METHODS

This is a retrospective study of data collected as part of a project to determine reference limits for clinical practice at the Radboud University Medical Center, Nijmegen, The Netherlands, and was, therefore, exempt from ethical approval. All subjects provided their informed consent and procedures were performed in accordance with the ethical standards as laid down in the declaration of Helsinki. Ultrasound examinations were carried out by five laboratory technicians, each with 5–10 y of experience in muscle ultrasound.

Sample size estimation yielded a need for 80 subjects for regression-based reference limits.[8] A decision was made to aim to enroll 10 healthy subjects, 5 males and 5 females, for each 10 y age category to ensure a balanced age and sex distribution. Subjects with

TABLE 1 Subject characteristics and outcomes for different categories

Category	Sex (M/F)	Age (y)	BMI (kg/m^2)	Echogenicity (0–255)	Thickening ratio	$T_{end\text{-}exp}$ (mm)	$T_{end\text{-}insp}$ (mm)
Age (y): 0–9	7/5	6.2 (2.3)	16.6 (2.8)	56.9 (9.1)	2.4 (0.5)	1.4 (0.4)	3.2 (0.7)
Age (y): 10–19	4/6	16.5 (3.6)	19.0 (2.4)	64.5 (8.9)	2.6 (0.5)	1.3 (0.4)	3.3 (0.6)
Age (y): 20–29	6/6	24.7 (3.1)	21.6 (2.1)	67.2 (7.8)	2.3 (0.6)	1.6 (0.4)	3.5 (1.1)
Age (y): 30–39	5/5	35.3 (2.8)	23.0 (3.0)	69.8 (15.8)	2.5 (0.5)	1.6 (0.5)	3.8 (1.2)
Age (y): 40–49	5/5	45.9 (2.9)	23.7 (2.9)	76.7 (13.6)	2.4 (0.6)	1.5 (0.4)	3.4 (1.1)
Age (y): 50–59	4/5	55.9 (2.3)	24.3 (2.1)	75.3 (14.2)	2.6 (0.5)	1.5 (0.4)	3.8 (0.9)
Age (y): 60–69	5/6	65.4 (3.0)	24.3 (4.3)	81.4 (9.5)	2.4 (0.7)	1.4 (0.4)	3.3 (0.7)
Age (y): 70–80	4/5	74.3 (3.3)	23.0 (1.8)	84.3 (14.8)	2.2 (0.6)	1.8 (0.3)	4.1 (1.4)
Sex: M	40/0	38.2 (23.0)	21.8 (4.0)	70.4 (13.5)	2.5 (0.6)	1.6 (0.5)	3.8 (1.0)
Sex: F	0/43	39.7 (23.2)	21.8 (3.6)	72.3 (15.0)	2.3 (0.5)	1.4 (0.3)	3.2 (0.9)
Age (y): 0–19	9/8	10.9 (6.0)	17.7 (2.8)	60.1 (9.6)	2.5 (0.5)	1.4 (0.4)	3.3 (0.7)
Age (y): 20–80	31/35	49.2 (17.6)	23.3 (2.9)	75.5 (13.5)	2.4 (0.6)	1.6 (0.4)	3.6 (1.1)
Sex: M, age (y): 0–19	9/0	11.2 (5.4)	17.7 (3.2)	60.3 (6.2)	2.6 (0.6)	1.4 (0.5)	3.5 (0.7)
Sex: M, age (y): 20–80	29/0	48.5 (18.1)	23.3 (3.1)	74.2 (13.6)	2.5 (0.6)	1.7 (0.5)	4.0 (1.1)
Sex: F, age (y): 0–19	0/9	10.6 (6.8)	17.7 (2.5)	60.0 (12.2)	2.3 (0.3)	1.3 (0.2)	3.0 (0.6)
Sex: F, age (y): 20–80	0/32	49.8 (17.5)	23.2 (2.8)	76.7 (13.6)	2.3 (0.6)	1.4 (0.3)	3.3 (1.0)
Total	40/43	39.0 (22.9)	21.8 (3.8)	71.4 (14.3)	2.4 (0.6)	1.5 (0.4)	3.5 (1.0)

Note: Data are presented as mean (SD). Total mean values were used to center age and BMI.

any condition affecting the respiratory or skeletal muscle system were excluded. Demographic factors including age, sex, and BMI were collected. Subjects were recruited via advertisements on social media.

An Esaote MyLab Twice ultrasound machine (Esaote SpA, Genoa, Italy) equipped with a 3–13 MHz LA533 linear transducer was used to assess diaphragm thickness at resting end-expiration ($T_{end\text{-}exp}$) and at maximal end-inspiration ($T_{max\text{-}insp}$). Measurements were performed according to previously published methodology (See Supporting Information Methods, which are available online).[9] Thickening ratio was calculated as $T_{max\text{-}insp}$ divided by $T_{end\text{-}exp}$.

Diaphragm echogenicity values were calculated from the images used for measurements of $T_{end\text{-}exp}$. Using custom developed software in Matlab (R2018a, Mathworks, Natick, MA, USA) and the trace method, a region-of-interest of diaphragm muscular tissue was manually selected.[10] Echogenicity was calculated as the mean pixel grayvalue of this region-of-interest and averaged over three measurements.

After checking linearity, independency, homoscedasticity, and normality, a stepwise multivariate linear regression was performed for echogenicity, thickening ratio, $T_{end\text{-}exp}$, and $T_{max\text{-}insp}$ using R software.[11] A full factorial model was explored with age, sex, and BMI as covariates and their quadratic terms. To uphold independence between the covariates and their quadratic terms, age and BMI were centered. Akaike's information criterion (AIC) was used to determine the best fit.[12] This approach allows covariates to be included in the final regression model when they have considerable impact on model fit, even when there is no significant association between the covariate and the dependent variable.

Intraclass correlation coefficients (ICCs) were calculated on the three repeated measures during one session to assess intra-rater reliability. ICC values below 0.50 were considered as poor reliability, 0.50–0.75 moderate, 0.76–0.90 good, and 0.91–1.00 excellent.[13]

TABLE 2 Regression models fitted to echogenicity, thickening ratio, $T_{end\text{-}exp}$, and $T_{max\text{-}insp}$

Outcome	Regression formula
Echogenicity	$71.443 + 0.390 * cAge$
Thickening ratio	$2.560 - 0.056 * cBMI + 0.006 * cAge + 0.0003 * cAge^2$
$T_{end\text{-}exp}$	$1.325 + 0.041 * cBMI + 0.211 * Sex(M) + 0.0001 * cAge^2$
$T_{max\text{-}insp}$	$3.237 + 0.049 * cBMI + 0.613 * Sex(M)$

Note: cAge: centered age, calculated by subtracting 39.0 from age in years. cBMI: centered BMI, calculated by subtracting 21.8 from BMI in kg/m^2. cAge^2: centered age squared.

3 | RESULTS

83 healthy subjects were recruited, as listed in Table 1. $T_{max\text{-}insp}$ was missing in one subject. Four diaphragms, with a $T_{end\text{-}exp}$ <1 mm, were too thin to permit determination of a reliable region-of-interest, and were excluded from echogenicity analysis.

Table 2 and Figure 1 present the regression analyses, and the specifications are presented in the supplement. Group average values were different between sexes for $T_{end\text{-}exp}$and $T_{max\text{-}insp}$. An increase in age was associated with an increase in echogenicity. Age and age squared were not associated with thickening ratio, although they were included in the regression model based on AIC. An increase in BMI

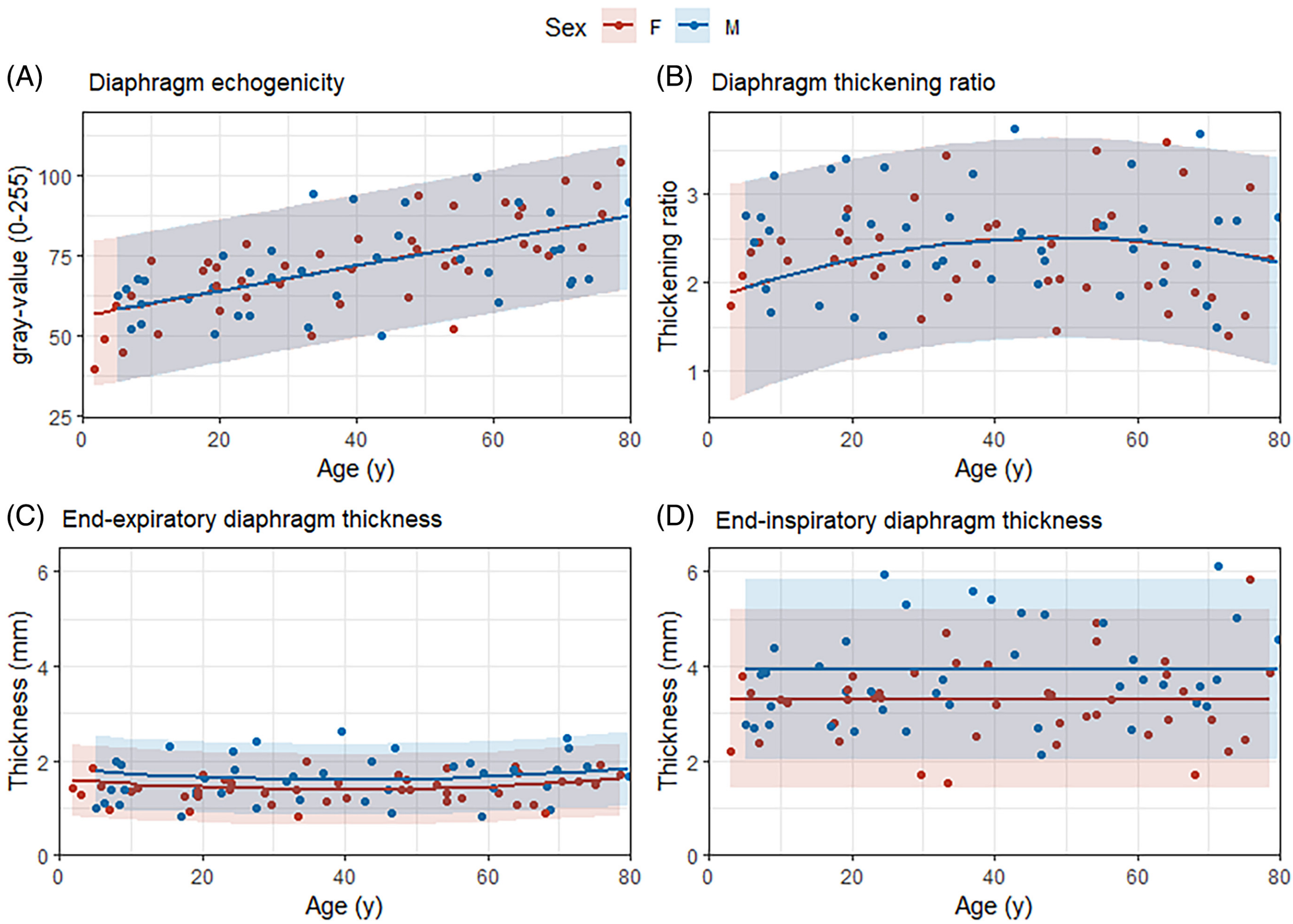

FIGURE 1 Graphical representation of fitted regression models. Each dot represent the measurement of a single subject, the line represents predicted values for each subject, where BMI was set fixed at the adult group mean of 23.3 kg/m^2, and the shaded area represents the 95% prediction interval. A, Diaphragm echogenicity. B, Diaphragm thickening ratio. C, End-expiratory diaphragm thickness. D, End-inspiratory diaphragm thickness

was associated with an increase in thickening ratio and a decrease in $T_{end\text{-}exp}$.

Intra-observer reliability of the three echogenicity measurements, $T_{end\text{-}exp}$and $T_{max\text{-}insp}$ were all excellent, with ICCs of 0.93 (0.89–0.96), 0.92 (0.89–0.94), and 0.93 (0.91–0.95), respectively.

4 | DISCUSSION

In healthy subject across a wide age range, we found that diaphragm thickness and thickening do not change with age, whereas diaphragm echogenicity increases with age. Sex and BMI have small effects on diaphragm thickness, but not on diaphragm thickening.

Diaphragm thickness and thickening ratio values presented in this study are comparable to previously reported values.[14–18] Interestingly, Boon and colleagues, using an apparently similar approach reported a $T_{end\text{-}exp}$ of 3.3 mm compared to 1.6 mm in our adult population.[9] Note that BMI in our adult population was considerably lower (23.3 vs. 27.2 kg/m^2). Although we and others[9,19] found an association between BMI and diaphragm thickness, this cannot fully explain the relatively large difference. Small differences in methodology may also contribute to differences in thickness. The variability in reported values for diaphragm thickness highlights the importance of collecting center-specific normative values. The larger variation in $T_{max\text{-}insp}$ compared to $T_{end\text{-}exp}$ is in accordance with other reports.[20] This may be attributed to variation in subjects' performance of the maneuver to take a deep breath and affects the level of diaphragm recruitment and the anatomical position of the diaphragm relative to the ultrasound probe.

Our study shows that diaphragm thickness is constant over a wide age range. This differs from skeletal limb muscles that generally increase in thickness until 30–40 y, after which muscle thickness decreases (sarcopenia).[7] Apparently, changes in respiratory demand with aging, for example due to decreased respiratory compliance, do not seem to be accompanied by changes in diaphragm muscle mass but other mechanisms, like changes in motor control.[21]

In agreement with previous studies, diaphragm thickness was larger in men than women.[9,15,20] The calculation of thickening ratio cancels out sex differences. We also identified BMI as significant predictor of $T_{end\text{-}exp}$ and thickening ratio, but the size of this effect was small. The latter may result from the narrow range of BMI in our adult population (23.3 ± 2.9 kg/m^2). It has been shown that outside this range BMI has larger effects on diaphragm thickness and thickening ratio.[19] Overall, little variance in thickening ratio was explained by our regression model. Thus, the lower limit of normal (5th percentile) of our healthy population, ie, 1.6, can be used as cut off value for a normal diaphragm thickening ratio regardless of the subjects' age, sex, and BMI.[22]

The absence of changes in diaphragm thickening with age is in apparent contrast to age-related changes in pulmonary function and respiratory muscle strength.[23,24] Furthermore, diaphragm function, as assessed with transdiaphragmatic pressure, is only weakly correlated with diaphragm thickening.[25] Therefore, the relationship between the pressure generating capacity of the diaphragm and diaphragm thickening warrants further research. This may be better reflected by other ultrasound modes such as strain imaging or shear wave elastography.[26,27]

Different ultrasound devices produce different grayscale images, meaning that our diaphragm echogenicity values cannot be used with different ultrasound devices.[5,28] However, the observed association with age is expected to exist with values obtained from a different machine, as sarcopenia is an inherent property of aging muscle.[7] Normative values should be collected for each different ultrasound device, and age-matched controls should be included when normative values are unavailable. For example, a recent study on diaphragm echogenicity compared mechanically ventilated patients, median age 59 y, with healthy controls, median age 27 y.[29] Our data imply that such a comparison is likely not valid. Furthermore, multiple ultrasound devices were used, complicating comparison of echogenicity values.

This study has limitations. First, the range in BMI was narrow. This impairs the interpretation of diaphragm ultrasound data of a patient outside this range. Second, normative data as presented in this study may have low generalizability to other centers. However, the associations with age, sex, and BMI are independent of measurement technique and device settings.

5 | CONCLUSIONS

The associations between diaphragm thickness, thickening, and echogenicity and age, BMI, and sex highlight the importance of taking subject characteristics into account when interpreting diaphragm ultrasound measurements in clinical practice and research.

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CONFLICT OF INTEREST

Nens van Alfen works as an ultrasound consultant for Dynacure and performs editorial services for Wiley Publishing Inc; all payments go to their employer. The remaining authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

STATEMENT ON ETHICAL PUBLICATION

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

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A novel method to measure sensory nerve conduction of the posterior antebrachial cutaneous nerve

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Abstract

Introduction/Aims: Posterior antebrachial cutaneous (PABC) nerve conduction studies could be useful for distinguishing PABC neuropathy from C7 radiculopathy. In the conventional method using an antidromic method, the sensory nerve action potential (SNAP) is sometimes followed by a large volume-conducted motor potential. In this report we describe a reliable nerve conduction study using an orthodromic method for recording SNAPs of the PABC nerve.

Methods: Thirty-six healthy volunteers participated in this study. PABC SNAPs were recorded by placing a surface-active electrode 2 cm anterior to the lateral epicondyle. The PABC nerve was stimulated 10 cm distal to the active recording

Abbreviations: CV, coefficient of variation; NCS, nerve conduction study; PABC, posterior antebrachial cutaneous; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential.

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