Original Article

Diaphragm ultrasound in patients with prolonged weaning from mechanical ventilation

Sebastian Johannes Fritsch[1,2]^, Anna Große Siemer[1,3], Michael Dreher[4]^, Tim-Philipp Simon[1], Gernot Marx[1]^, Johannes Bickenbach[1]^

[1]Department of Intensive Care Medicine, University Hospital Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen, Aachen, Germany; [2]Jülich Supercomputing Centre, Forschungszentrum Jülich, Jülich, Germany; [3]Department of Neurology, Protestant Hospital Oldenburg, Oldenburg, Germany; [4]Department of Pneumology and Intensive Care Medicine, University Hospital Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen, Aachen, Germany

Contributions: (I) Conception and design: SJ Fritsch, J Bickenbach; (II) Administrative support: J Bickenbach; (III) Provision of study materials or patients: M Dreher, TP Simon, G Marx, J Bickenbach; (IV) Collection and assembly of data: AG Siemer; (V) Data analysis and interpretation: SJ Fritsch, AG Siemer, J Bickenbach; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Sebastian Johannes Fritsch, MD. Department of Intensive Care Medicine, University Hospital Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen, Pauwelsstr. 30, 52074 Aachen, Germany; Jülich Supercomputing Centre, Forschungszentrum Jülich, 52425 Jülich, Germany. Email: sfritsch@ukaachen.de.

Background: Several publications have examined diaphragmatic ultrasound using two-dimensional (2D) parameters in the context of weaning from mechanical ventilation (MV) and extubation. However, the studied cohorts had rather short duration of ventilation. Examinations on patients with prolonged weaning after long-term ventilation were missing. It was the aim of this study to assess of the diaphragm and peripheral musculature of patients undergoing prolonged weaning creating a chronological sequence of ultrasonic parameters during the course of weaning.

Methods: This study was carried out as a monocentric, prospective observational cross-sectional study. Patients in prolonged weaning who were transferred to a specialized weaning unit were eligible for inclusion if they were ventilated invasively by means of an endotracheal tube or tracheal cannula and if their expected treatment period was at least 5 days. Diaphragmatic function and one representative peripheral muscle were examined in 50 patients between March 2020 and April 2021. The 2D sonographic parameters of diaphragm and diaphragmatic function consisted of diaphragmatic thickness (Tdi) at the end of inspiration and expiration, the fractional thickening (FT) and the diaphragmatic excursion. Additionally, the M. quadriceps femoris was sonographically assessed at two locations. The difference of measurements between the first and the last measuring timepoint were examined using the Wilcoxon signed-rank test. For a longer chronological sequence, the Friedman's rank sum test with subsequent Wilcoxon-Nemenyi-McDonald-Thompson test for multiple comparisons was carried out.

Results: Fifty patients with prolonged weaning were included. The median duration of MV before transfer to the weaning unit was 11.5 [interquartile range (IQR) 10] days. Forty-one patients could be assessed over the full course of weaning, with 38 successfully weaned. Within these 41 patients, the sonographic parameters of the diaphragm slightly increased over the course of weaning indicating an increase in thickness and mobility. Especially parameters which represented an active movement reached statistical significance, i.e., inspiratory Tdi when assessed under spontaneous breathing [begin 3.41 (0.99) *vs.* end 3.43 (1.31) mm; P=0.01] and diaphragmatic excursion [begin 0.7 (0.8) *vs.* end 0.9 (0.6) cm; P=0.01]. The

^ ORCID: Sebastian Johannes Fritsch, 0000-0002-8350-8584; Michael Dreher, 0000-0002-3452-5329; Gernot Marx, 0000-0003-0866-4234; Johannes Bickenbach, 0000-0002-0039-8448.

presence of positive end-expiratory pressure (PEEP) and pressure support did not influence the sonographic parameters significantly. The M. quadriceps femoris, in contrast, decreased slightly but constantly over the time [lower third: begin 1.36 (0.48) *vs.* end 1.28 (0.36) cm; P=0.054].

Conclusions: The present study is the first one to longitudinally analyse diaphragmatic ultrasound in patients with prolonged weaning. Sonographic assessment showed that Tdi and excursion increased over the course of prolonged weaning, while the diameter of a representative peripheral muscle decreased. However, the changes are rather small, and data show a wide dispersion. To allow a potential, standardized use of diaphragm ultrasound for diagnostic decision support in prolonged weaning, further studies in this specific patient group are required.

Keywords: Diaphragm; ultrasound; ultrasonography; ventilator weaning; prolonged weaning

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Introduction

The diaphragm represents the most important respiratory muscle. During normal tidal breathing, it can contribute with up to 80% of the breathing work (1). However, due to its anatomical configuration and its location, it shows poor accessibility to diagnostic procedures. An appropriate assessment of the diaphragmatic function consists of measurement of transdiaphragmatic pressure (Pdi), electric activity of the diaphragm (EAdi) and diaphragmatic imaging with fluoroscopy (2). Despite being considered as gold standard, all these techniques have several drawbacks limiting their applicability in daily routine.

Nevertheless, there is a dedicated interest to have a technique at hand, which allows the physician at the bedside making a clear and reliable statement regarding the diaphragmatic function. Due to this gap in our diagnostic toolbox, ultrasound has attracted much attention. It is non-invasive, broadly available at the bedside, easy to learn, quick to perform, well-tolerated and shows practically no unintended side effects. For the evaluation of the diaphragm, the majority of previous publications mainly focussed on two-dimensional (2D) measurement techniques, i.e., the diaphragmatic thickness (Tdi) at inspiration and expiration, the fractional thickening (FT) or the diaphragmatic excursion (3-5).

The need for a reliable diagnostic technique applies especially for cases, where the diaphragm is no longer working properly. Such a highly relevant condition is ventilator-induced diaphragmatic dysfunction (VIDD). Previous publications reported an incidence of VIDD of up to two thirds of patients under mechanical ventilation (MV) already after 24 hours (6). This pathophysiological complex condition results not only in an imbalance between diaphragmatic protein synthesis and degradation, but also in an impaired contractility due to changes in the intracellular calcium homoeostasis (7). Since the extent of VIDD correlates with the duration of MV, it is also strongly associated with weaning failure and increased mortality (8-12). A patient group, which can be considered as affected by VIDD by practically 100%, are patients in prolonged weaning from MV (13). According to the classification of Boles *et al.*, patients who are in prolonged weaning, require more than three spontaneous breathing trials (SBTs) or stay under MV for more than 7 days after the first SBT (14). The treatment of patients in prolonged weaning is frequently complex requiring multimodal and multi-professional treatment and should, thus, preferably be carried out in specialised weaning centres, which were established in several countries to increase the rate of successful weaning (15-17). Although the diaphragm exhibits special properties distinguishing it from other skeletal muscles (18), the peripheral musculature of patients in prolonged weaning is strongly affected as well. Current literature reports about one third of all intensive care unit (ICU) patients to suffer from a condition which is called ICU-acquired weakness (ICUAW), although it strongly depends on the age, sex, primary diseases, and treatment (19-21). In prolonged weaning, the proportion of ICUAW patients was given with 50% (13). It is often associated with muscle wasting and clinically characterized primarily by generalized, symmetric proximally emphasized extremity weakness (22). The fact that atrophy of the diaphragm and peripheral muscles in intensive care patients does not necessarily occur together, but can also be observed independently of each other (23), suggests that the atrophy of both muscle groups also occurs via different mechanisms.

Although several authors examined the ultrasound of diaphragm in the context of terminating an MV, most studies included patients with rather short MV duration and endotracheal intubation (24-27). In contrast, patients in prolonged weaning frequently are under MV for more than 2 weeks and underwent tracheostomy before admission to a specialized weaning unit. Ultrasonic evaluations of diaphragms of this special patient group are still sparse.

Therefore, the aim of our study was to conduct a prospective observational study performing sonographic assessment of the diaphragm in patients undergoing prolonged weaning. We aimed to create a chronological sequence of the ultrasonic parameters during the weaning progress carrying out several scheduled examinations. These sonographic results were analysed with respect to the diaphragmatic performance and patient specific conditions. Additionally, the study aimed to characterize not only the behaviour of diaphragmatic but also peripheral skeletal musculature during the course of weaning. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1712/rc).

Methods

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of the Faculty of Medicine, University Hospital Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen, Aachen, Germany (No. EK 402/19, 29.02.2020) and was registered at the German Clinical Trials Register (No. DRKS00020937). Written informed consent was taken from all individual participants or their health care proxy or legal guardian, if a patient was unable to give consent himself/herself. As soon as independent consent by the patient was possible again at a later point in time, this was subsequently obtained. Study participation and data collection and could be stopped at any time at the explicit request of the patient or representative. Data already collected were deleted at explicit request, otherwise data before withdrawal were included into the analysis.

Study design and patient selection

This study was carried out as a monocentric, prospective observational cross-sectional study. The size of the sample to be studied was set at 50 patients as a convenience sample. Due to a lack of data that could have been transferrable to our population, proper sample size planning was not possible.

Patients in prolonged weaning group 3 according to Boles *et al.* (14) who were transferred from an acute intensive care unit (ICU) to the specialised weaning unit of the University Hospital RWTH Aachen were eligible for inclusion into the study if they were ventilated invasively by means of an endotracheal tube or tracheal cannula and if they had an expected treatment period of at least 5 days in the weaning unit. Exclusion criteria encompassed age below 18 years, pregnancy, known pre-existing neuromuscular diseases or pareses affecting the diaphragm and rib fractures or surgical wounds, as well as dressings and drains in the area of examination. Patients who were admitted to the weaning unit from an out-of-hospital respiratory care facility were excluded as well. Since coronavirus disease 2019 (COVID-19) only became relevant as a medical condition after the start of the study, acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was also post hoc defined as an exclusion criterion in order to minimize health risks for the study personnel.

Data collection

Data collection was carried out between March 04, 2020 and April 03, 2021 on the specialized weaning unit of the University Hospital RWTH Aachen. At admission on the weaning unit, biometric data (age, sex, height and weight), the admission diagnosis, relevant pre-existing medical conditions and the MV duration before admission were recorded. At every single sonographic assessment, a set of respirator settings, respiratory parameters, and the duration of respiratory free time within the last 24 hours was recorded. For ventilator settings and respiratory parameters, the values which were next to the time of assessment were recorded if the patient breathed spontaneously at that time. The respective data were extracted from an electronic patient record system (medico//s, Siemens, Germany) and from an online patient data management system (IntelliSpace Critical Care and Anesthesia, ICCA Rev. F.01.01.001, Philips Electronics, Netherlands).

The outcome parameter 'successful weaning' was defined as the achievement of a continuous respirator-free time of 24 hours. Weaning failure, in contrast, included either death of the patient or a discharge with an out-of-hospital, both invasive as well as non-invasive MV following the treatment on the weaning unit. Reasons for termination of measurements included transfer to a rehabilitation facility or other hospital before the weaning process was fully completed with the intention to continue the weaning process there. For these patients, no data regarding the final outcome were available. Patient-related data were pseudonymized using a letter-number combination.

Examination schedule

The first ultrasound examination was performed on the day of inclusion and was subsequently repeated at 72-hour intervals until the patient met the criteria for weaning success or failure. Whenever possible, examinations were carried out under MV in an assisted spontaneous breathing mode as well as during a SBT without assistance within a T-piece trial, unless there were nursing or patient-related reasons suggesting otherwise.

Sonographic assessment

Ultrasound device and user

Ultrasonic examinations were performed with the portable ultrasound device "Lumify" from Philips (Amsterdam, The Netherlands) by a trained examiner (A.G.S.) under intermittent supervision of a physician with several years of experience with diaphragmatic ultrasound. To increase validity and comparability of data, the examinations were always performed at the same time of day. Additionally, the positions of transducer were marked using felt-tip markers on a transparent adhesive sheet for subsequent recordings.

Examination of diaphragm thickness and FT

Tdi and FT were evaluated using a broadband linear transducer (4–12 MHz) in B-mode. The transducer was placed in the zone of apposition in the area of the right hemithorax between the anterior and the middle axillary line at the level of the 8th–11th intercostal space. The diaphragm was shown here to be an echo-poor structure bordered by two echo rich lines representing peritoneum and pleura. The penetration depth and focus were adjusted to show the diaphragm in focus at the centre of the image. The transducer was held parallel to the longitudinal axis of the body. Tdi was measured at the same anatomic position following the longitudinal downward motion of the respective location over all breaths of one measurement. Tdi was recorded at the end of inspiration (Tdi_{insp}) and of expiration (Tdi_{exp}). FT was calculated using the following equation: $(Tdi_{insp} - Tdi_{exp})/Tdi_{exp}$.

Examination of the diaphragm excursion

The measurement was performed with a broadband sector transducer (1–4 MHz) in B-mode. The transducer was placed just below the right costal arch between the medioclavicular line and the anterior axillary line and aligned to create a perpendicular slice through the posterior third of the diaphragm. The transducer was held parallel to the intercostal spaces, and the liver served as sonographic window. The diaphragm appeared in B-mode as an anechoic contour dorsal to the liver. The penetration depth was selected so that the diaphragm could be imaged optimally. The optimal location for placement of the measurement line was then determined in B-mode. Subsequently, the movement of the anatomical structures was analysed in M-mode. The depth difference between inspiration and expiration (represented by minima and maxima of the resulting curve) represented the excursion of the diaphragm caudally during a breath.

Examination of the quadriceps femoris muscle

The measurement was performed with a broadband convex transducer (2–5 MHz) in B-mode. The transducer was placed both on the half as well as between the lower and the two upper thirds of a line between the upper edge of the patella and the spina iliaca anterior superior. The correct position was established by measuring distances with a tape measure and marking the position with a felt-tip marker. The transducer was placed on the top of the femur perpendicular to the femur, creating a transverse section through the femur. The thickness of the M. quadriceps femoris was defined as the distance between the upper edge of the femur and the uppermost muscle fascia.

Statistical analysis

Statistical analysis of the data was performed using SAS® statistical software version 9.4 (SAS Institute Inc., Cary, USA). Descriptive analysis of the biometric and medical data was performed by specifying the absolute (n) and relative (%) frequencies and determining the median and interquartile range (IQR). The difference of measurements between the first and the last measuring timepoint were examined using the Wilcoxon signed-rank test. For

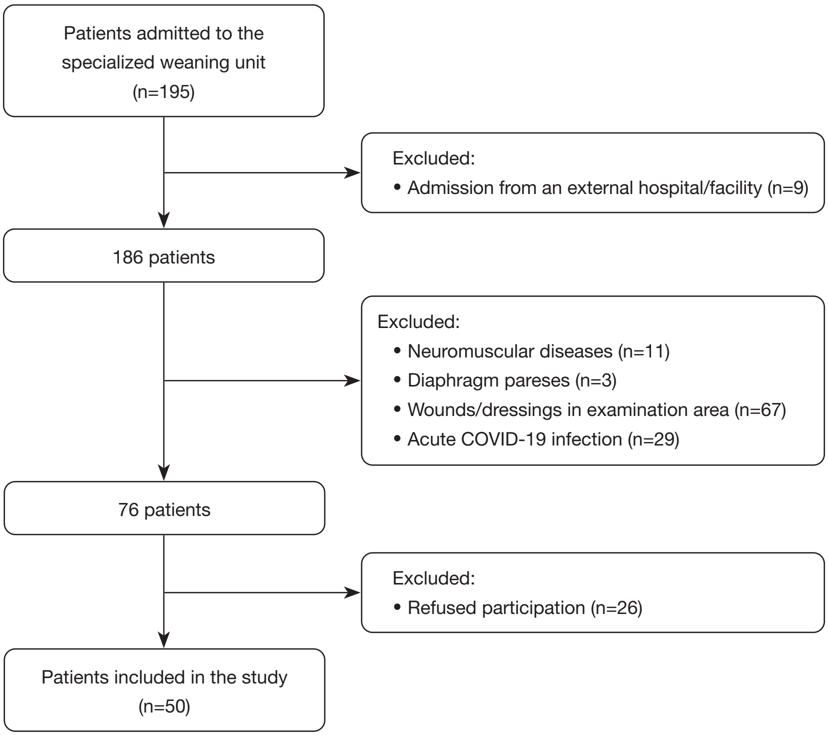

Figure 1 Flow diagram of the exclusion process from screening to final inclusion of patients in the study according to eligibility criteria indicating the reasons to exclude patients and the respective numbers. COVID-19, coronavirus disease 2019.

patients, whose measurements were terminated before completion of the weaning process (transfer to other facility, withdrawal of consent), the last measured data were not included to the analysis. In order to analyse the influence of whether a measurement was taken under MV or under spontaneous breathing, pairs of all measurements were formed that were available at a certain time point under both MV and spontaneous breathing and the difference between the two values was calculated. The question of whether significant differences existed was tested using the Wilcoxon signed rank test. To allow an appropriate analysis of the sonographic parameters during a longer course of weaning, a mean value of the measurements with and without respirator at a certain point in time were calculated. Since the individual duration of weaning differed in every patient, the duration was separated into three parts and four measurements were chosen for analysis. These measurements consisted of the first and the last recorded measurement and the respective measurements which were next to the separation points. In further analyses, the first three measurements after admission to the weaning ward and the last three measurements before end of the weaning process were examined. Patients with less than four or three measurements respectively were excluded from these analyses. The analysis for significant differences between the different timepoints was carried out using a Friedman's rank sum test. In case of a significant result of the Friedman test, a Wilcoxon-Nemenyi-McDonald-Thompson test for multiple comparisons was calculated using a SAS macro (28). A two-sided P value of less than 0.05 was deemed significant.

Results

Patient characteristics

During the inclusion period, 195 patients were admitted to the specialized weaning unit. A flow diagram of the exclusion process from screening to final inclusion of patients in the study according to eligibility criteria is indicated in *Figure 1*. Fifty patients with a median age of 64.5 years (IQR 17 years) were included into the study. Thirty-two patients (64%) were male. All patients were ventilated invasively via tracheal cannula. Of these 50 patients, 38 patients (76%) could be weaned successfully from MV. Three patients underwent weaning failure consisting of two patients who died on the weaning unit

Table 1 Clinical characteristics of the 50 patients included in the study

Parameter	Median [IQR] or n [%]
Age (y)	64.5 [17]
Male sex	32 [64]
Height (cm)	172 [12]
Weight (kg)	83.5 [20]
Admitting department	
Internal medicine	11 [22]
Cardiac and thoracic surgery	22 [44]
Neurosurgery	6 [12]
Vascular surgery	5 [10]
Other surgical departments	6 [12]
Admission diagnosis	
Respiratory failure after surgery of …	
Coronary arteries, heart valves or aorta	25 [50]
Lung	2 [4]
Abdomen	2 [4]
Respiratory failure due to pulmonary pathology	
ARDS	2 [4]
Other	2 [4]
Intracranial bleeding and traumatic brain injury	6 [12]
Cardiogenic shock	7 [14]
Other diagnoses	4 [8]
Preexisting conditions	
COPD	6 [12]
Asthma	1 [2]
Congestive heart failure	8 [16]
Diagnosis during hospital stay	
ARDS	13 [26]
Sepsis	20 [40]
Pneumonia	39 [78]
ICUAW	13 [26]
Duration of MV on ICU before admission on weaning unit (d)	11.5 [10]
Duration of weaning (d)	13.5 [9]
Weaning outcome	
Successful weaning	38 [76]
Weaning failure	
Discharge with NIV	1 [2]
Death	2 [4]
Transfer to external rehabilitation facility	7 [14]
COVID-19 infection during study	1 [2]
Withdrawal of consent	1 [2]

IQR, interquartile ratio; y, years; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ICUAW, ICU-acquired weakness; MV, mechanical ventilation; ICU, intensive care unit; d, days; NIV, non-invasive ventilation; COVID-19, coronavirus disease 2019.

and one patient who was discharged with the need for an intermittent non-invasive ventilation. Seven patients were transferred to other facilities with invasive MV. One patient's representative withdrew consent for further examinations and one patient developed an infection with COVID-19 during the measurement, thus for these patients no further measurements were carried out. For the latter nine patients a weaning outcome is not determinable.

The median length of stay on the weaning unit was 13.5 (IQR 9) days. Patients underwent MV during the preceding ICU stay for a median duration of 11.5 (IQR 10) days. For the respiratory parameters and respirator settings, please refer to Table S1. The full clinical characteristics are given in *Table 1*.

Sonographic parameters at begin and at completion of the weaning process

Over the course of weaning, all sonographic parameters for assessing the diaphragm increased at the median, as can be seen in *Figure 2*. While changes in Tdi_{exp} increased only minimally [without respiratory support: begin of weaning 2.95 (1.11) *vs.* end of weaning 3.10 (1.21) mm; P=0.10], Tdi_{insp} and consequently FT increased more markedly. For the measurement of Tdi_{insp} without respiratory assistance, the difference between beginning and end of

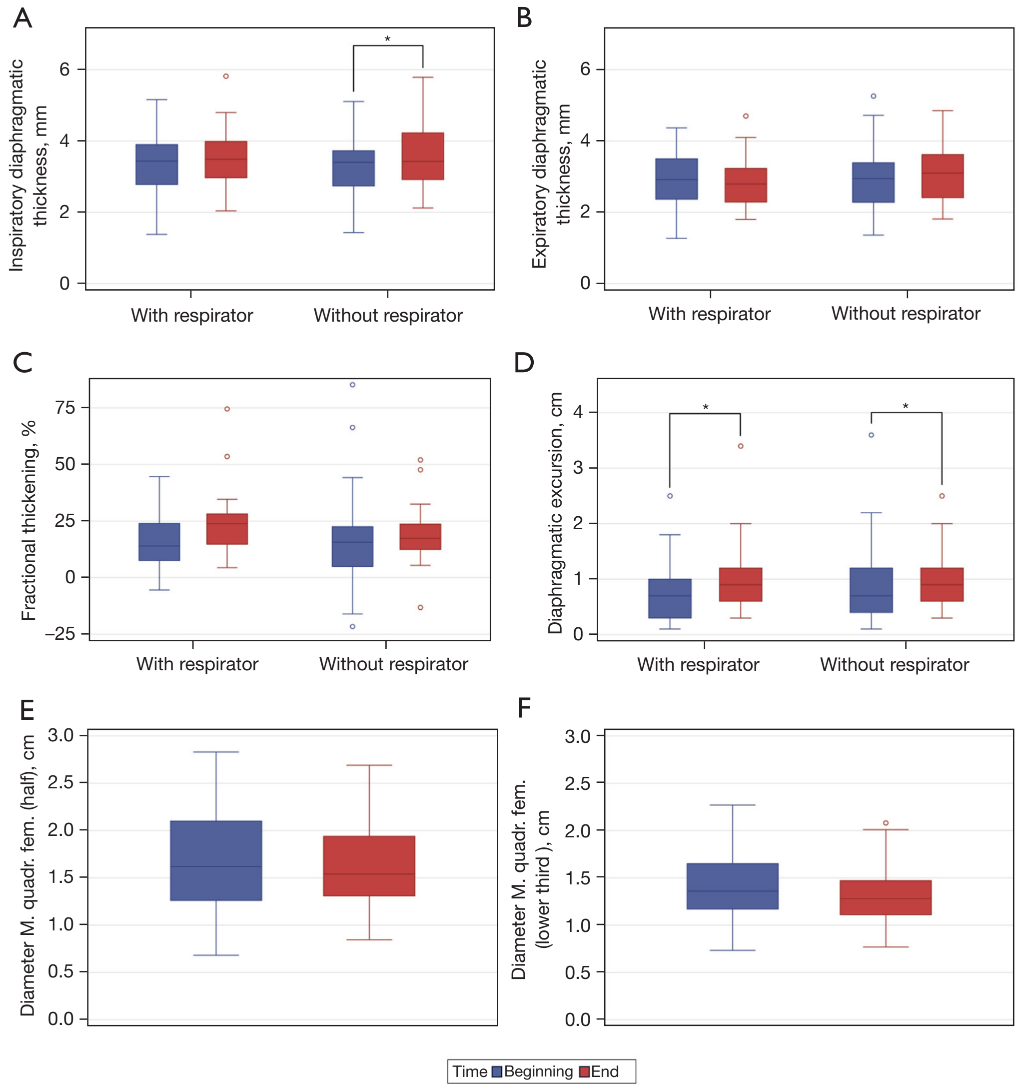

Figure 2 Sonographic assessment of diaphragm and peripheral musculature at the beginning and at the end of the weaning process. (A) Inspiratory diaphragmatic thickness. (B) Expiratory diaphragmatic thickness. (C) Fractional thickening. (D) Diaphragmatic excursion. (E,F) Diameter of the musculus quadriceps femoris measured on the half (E) as well as between the lower and the two upper thirds (F) of a line between patella and spina iliaca anterior superior. The box indicates the IQR and the median, the whiskers indicate 1.5 times the IQR and the dots indicate outliers. The blue boxes give the data at the beginning of weaning, while the red boxes represent the end of the weaning process. P values were calculated using the Wilcoxon signed rank test. *, P<0.05. IQR, interquartile range.

weaning reached statistical significance [without respiratory support: begin of weaning 3.41 (0.99) *vs.* end of weaning 3.43 (1.31) mm; P=0.01]. Additionally, for diaphragmatic excursion, a significant increase could be observed, as well with as without the respirator [without respiratory support: begin of weaning 0.7 (0.8) *vs.* end of weaning 0.9 (0.6) cm; P=0.01]. The peripheral musculature, on the other hand, represented by the thigh muscles, continued to show low values without an increase or in some cases even a decrease in the median diameter. This decrease was particularly apparent in the measurement in the lower third, even if statistical significance was slightly missed [lower third: begin of weaning 1.36 (0.48) *vs.* end of weaning 1.28 (0.36) cm; P=0.054]. For the full data, please refer to *Table 2*.

Table 2 Sonographic parameters at beginning and at end of weaning process

Sonographic parameter	Begin of weaning		End of weaning		Median of differences (end – begin)		P value
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
Inspiratory diaphragmatic thickness (mm)							
With respirator	48	3.44 (1.12)	28	3.49 (1.02)	28	0.24 (1.13)	0.24
Without respirator	46	3.41 (0.99)	41	3.43 (1.31)	39	0.37 (0.90)	0.01
Expiratory diaphragmatic thickness (mm)							
With respirator	48	2.92 (1.14)	28	2.80 (0.95)	28	0.08 (0.84)	0.68
Without respirator	46	2.95 (1.11)	41	3.10 (1.21)	39	0.12 (0.68)	0.10
Fractional thickening (%)							
With respirator	48	13.98 (16.40)	28	23.89 (13.47)	28	8.77 (21.70)	0.10
Without respirator	46	15.68 (17.62)	41	17.38 (11.18)	39	5.34 (22.52)	0.26
Excursion (cm)							
With respirator	44	0.7 (0.7)	27	0.9 (0.6)	27	0.2 (0.7)	0.03
Without respirator	43	0.7 (0.8)	38	0.9 (0.6)	36	0.2 (0.5)	0.01
M. quadr. fem. (half) (cm)	50	1.62 (0.84)	41	1.54 (0.63)	41	–0.004 (0.70)	0.46
M. quadr. fem. (lower third) (cm)	50	1.36 (0.48)	41	1.28 (0.36)	41	–0.07 (0.35)	0.054

The presence of a statistically significant difference between the two time points was examined using a Wilcoxon signed rank test. Significance level α=0.05. IQR, interquartile ratio; M. quadr. fem., musculus quadriceps femoris.

Comparison of diaphragmatic measurements with and without respiratory assistance

It was further analysed whether the presence of positive end-expiratory pressure (PEEP) and pressure support while the patient was connected to the ventilator had an influence on the sonographic assessment of the diaphragm. As shown in *Table 3*, there were no relevant differences between a measurement under respiratory support and under spontaneous breathing on a T-piece.

Sonographic parameters over the course of the weaning process

In a first step, an analysis of the complete weaning course was carried out (see *Table 4*). Similar to the results of the analysis which includes the first and the last measurement only, in the analysis over the complete course, the diaphragmatic excursion showed a significant change over the time [t_{begin}: 0.68 (0.5); $t_{0,33}$: 0.75 (0.55); $t_{0,66}$: 0.80 (0.65); t_{end}: 0.80 (0.55); P=0.008]. However, although the Friedman test showed a significant change, the post-hoc Nemenyi test failed to show significant pairwise comparisons. For the other parameters, the Friedman's test yielded no significant changes (see *Figure 3*).

In order to investigate whether relevant changes in the diaphragmatic architecture occured either immediately after the start of the structured weaning process or immediately before its completion, the first and last three measurements were also analysed in two separate steps. Over the first three measurements, the inspiratory Tdi showed a significant increase [t_{begin}: 2.58 (1.64); $t_{begin+1}$: 3.33 (1.33); $t_{begin+2}$: 3.54 (1.47); P=0.01] as well as the FT [t_{begin}: 15.03 (16.14); $t_{begin+1}$: 13.66 (19.59); $t_{begin+2}$: 18.42 (14.77); P=0.03]. In the post-hoc pairwise comparison, for inspiratory Tdi a significant result could be shown between the initial measurement and day 6 (P=0.004). The expiratory thickness and excursion increased as well, but without reaching significance (P=0.09 and P=0.056). At the end of the weaning, the excursion showed a significant increase over the last three measurements [t_{end-2}: 0.75 (0.75); t_{end-1}: 0.75 (0.8); t_{end}: 0.88 (0.55); P=0.03]. The results of the remaining parameters were inconclusive, also due to a strong increase of spread. The full analyses can be found in the Tables S2-S6.

Table 3 Influence of the respirator on the diaphragmatic assessment

Sonographic parameter	With respirator		Without respirator		Median of differences (with – without)		P value
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
Inspiratory diaphragmatic thickness (mm)	246	3.38 (1.22)	271	3.38 (1.13)	212	0.01 (0.67)	0.55
Expiratory diaphragmatic thickness (mm)	246	2.92 (0.96)	271	2.87 (1.13)	212	0.04 (0.62)	0.32
Fractional thickening (%)	246	13.95 (16.27)	271	15.77 (14.77)	212	−0.87 (17.87)	0.93
Excursion (cm])	220	0.6 (0.7)	249	0.7 (0.6)	189	0.00 (0.4)	0.89

Data of all measurements at a certain time point, for which measurements were available under both MV and spontaneous breathing. n represents the number of data points included in the analysis, i.e., the individual measurements at a certain point in time independent of their assignment to a specific patient. The presence of a statistically significant difference between the two time points was examined using a Wilcoxon signed rank test. Significance level α=0.05. IQR, interquartile ratio; MV, mechanical ventilation.

Table 4 Sonographic parameters over the course of weaning process

Sonographic parameter	Begin of weaning		1/3 of weaning course		2/3 of weaning course		End of weaning		P value
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
Inspiratory diaphragmatic thickness (mm)	38	3.37 (0.77)	38	3.45 (0.81)	38	3.46 (1.46)	38	3.42 (1.36)	0.15
Expiratory diaphragmatic thickness (mm)	38	2.85 (0.83)	38	3.02 (0.83)	38	2.97 (0.98)	38	3.06 (0.98)	0.36
Fractional thickening [%]	38	12.58 (16.78)	38	15.66 (16.48)	38	14.98 (14.30)	38	16.84 (12.28)	0.13
Excursion (cm)	34	0.68 (0.5)	36	0.75 (0.55)	36	0.80 (0.65)	36	0.80 (0.55)	0.008
M. quadr. fem. (half) (cm)	38	1.56 (0.81)	38	1.58 (0.69)	38	1.53 (0.67)	38	1.52 (0.53)	0.71
M. quadr. fem. (lower third) (cm)	38	1.28 (0.48)	38	1.25 (0.59)	38	1.24 (0.41)	38	1.26 (0.33)	0.54

The data consists of the averaged data with and without respirator at a given time point. The presence of a statistically significant difference over the course of time was examined using a Friedman rank sum test. Significance level α=0.05. IQR, interquartile ratio; M. quadr. fem., musculus quadriceps femoris.

Discussion

The present study has shown that sonographic parameters representing the dynamical functionality of the diaphragm, like the inspiratory Tdi, the FT or especially the diaphragmatic excursion, showed significant increases over the course of the weaning. The thickness of the resting muscle layer of the diaphragm during expiration itself did not relevantly change over the time. Moreover, the M. quadriceps femoris representing the peripheral muscles in the present study did not show an increase of its diameter over time.

Sonographic evaluation of the diaphragm

Several authors have found a good correlation between the 2D-sonographic parameters and the diaphragmatic function (29-33). Other authors, however, were unable to make out a direct correlation and, for instance, found no respiratory impairment in patients clinically despite sonographically impaired diaphragmatic function (24,34-37). Recent systematic reviews and meta-analyses have analysed the role of diaphragmatic ultrasound in predicting the success or failure of weaning in patients undergoing MV (38-41). Summarizing the recent publications, it is stated, that there is a clear trend indicating that higher values of Tdi, FT and diaphragmatic excursion correlate with a higher rate of successful weaning. Contrarily, low values of diaphragmatic excursion and FT are associated with the risk of extubation failure. However, it should be noted that there are no generally recognised cut-off values; rather, each publication defines its own ones. Additionally, in many cases, only a

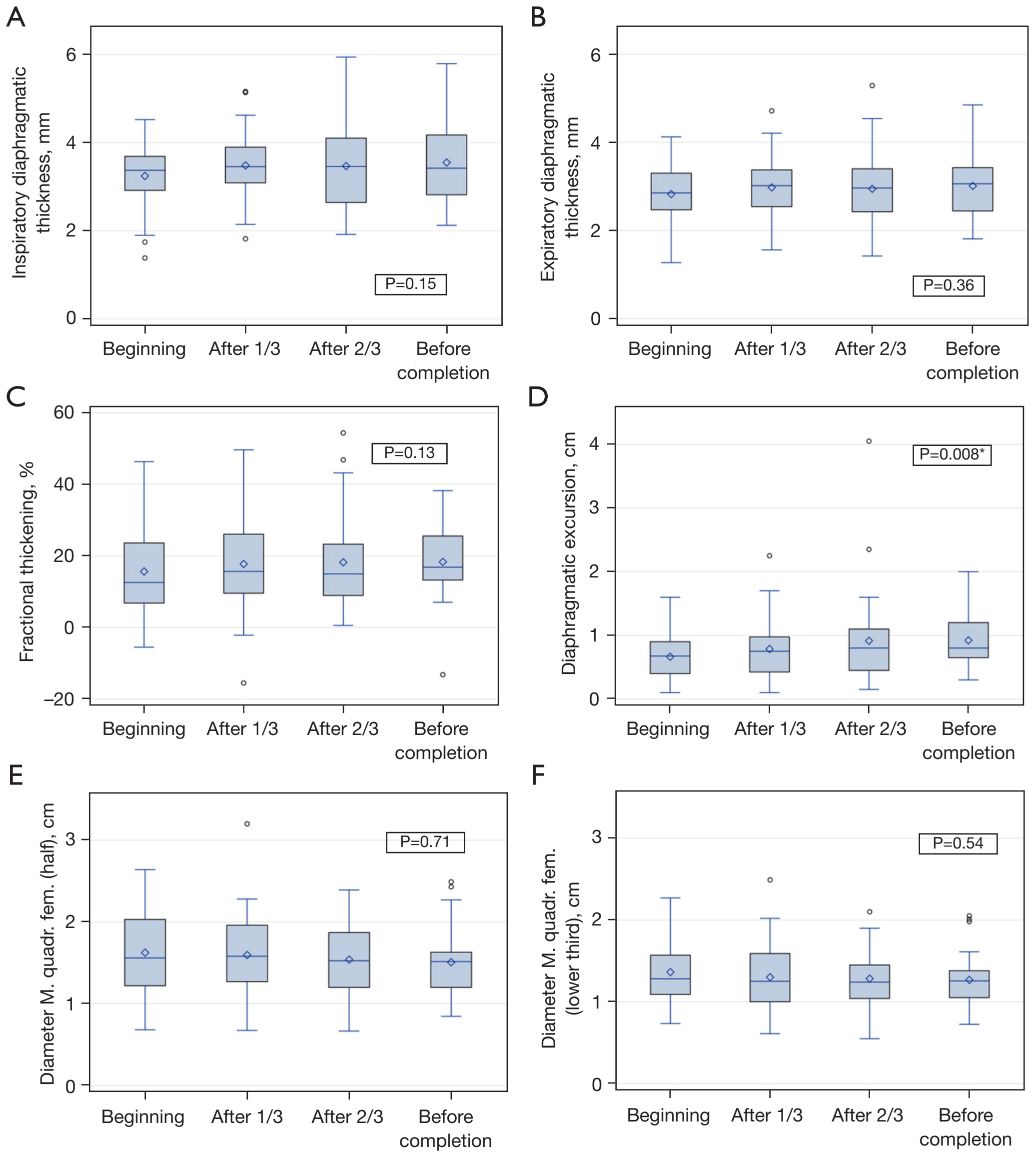

Figure 3 Sonographic assessment of diaphragm and peripheral musculature over the course of the weaning process. (A) Inspiratory diaphragmatic thickness. (B) Expiratory diaphragmatic thickness. (C) Fractional thickening. (D) Diaphragmatic excursion. (E,F) Diameter of the musculus quadriceps femoris measured on the half (E) as well as between the lower and the two upper thirds (F) of a line between patella and spina iliaca anterior superior. The box indicates the IQR and the median, the whiskers indicate 1.5 times the IQR and the dots indicate outliers. The line within the box indicates the median, while the diamond indicates the mean value. The measurements were derived at the beginning of the weaning process, after 1/3, after 2/3 and immediately before completion of the weaning. P values were calculated using the Friedman's rank sum test. *, P<0.05. IQR, interquartile range.

moderate sensitivity and specificity was reported. This is also underlined by the fact that Haaksma and colleagues found in their study that thoracic sonography had only a weak predictive value for the prediction of a successful extubation if the respective patient had undergone a successful SBT (42). Due to the very low number of patients with weaning failure in the present study, a respective analysis of the study cohort was not possible. However, many publications, for instance, choose a cut-off value of 20% or even 30% as predictor of weaning success for FT. In the present study, however, a relevant proportion of patients showed a FT below these cut-off values but could be weaned successfully. The same is true for the diaphragmatic excursion, whose cut-off value is frequently given with 1 cm. This value, as well, is not reached by a relevant part of patients in the present work. It must therefore be assumed that morphological changes during long-term MV occur, that alter the sonographic parameters but do not have an influence on the functionality of the diaphragm. This hypothesis is supported by a work of Poulard and colleagues, who could show that the FT stayed nearly unchanged for a long time, while the Pdi already showed strong increases under respiratory loading (43). However, the underlying disease that led to respiratory failure and prolonged weaning must also be taken into account. While the present study excluded COVID-19 patients, Vetrugno *et al.* investigated the role of FT in predicting weaning success (44). Although the time under MV before initiation of weaning was comparable between the population of the present and the COVID-19 study, COVID-19 patients had a dramatically worse weaning success rate and significantly lower Tdi values. In the COVID-19 study, the patients with weaning failure even showed a tendency towards higher FT values. This suggests that the highly acute mechanisms of an infectious disease damaging the respiratory system may be very different from chronic conditions such as end-stage COPD. Thus, it does not seem sufficient to generalize patients in prolonged weaning when examining diaphragm sonography, but to stratify the patients according to their specific underlying disease that led to prolonged weaning.

Already from a purely physical point of view alone, it is to be expected that the application of positive pressures to the lungs will lead to a change in intrathoracic volumes and, consequently, to a change in the anatomical configuration of the diaphragm. Jansen and colleagues have addressed this question with excellent quality in a magnetic resonance imaging (MRI) study. Due to the ability of MRI to image the entire diaphragm and not just a section as with ultrasound, they were able to show that an increase in PEEP leads to a caudal displacement of the diaphragm with a shortening of the muscular parts in the zone of apposition and a consequent increase in Tdi (45). This fact was also shown for different parameters in several studies whose patients, however, were healthy subjects or ventilated for only a few days (29,46-48). In contrast, the patients in the present study do not show a relevant difference in sonographic parameters with and without ventilatory support and PEEP. The reason for this behaviour is rather unclear since at least the passive effects of increased intrathoracic pressure should apply here as well. A possible explanation could be provided by the study of Jansen *et al.*, which showed that the changes in diaphragmatic geometry in the lower PEEP range were only very slight (45). In our study, too, the applied PEEP was 6 mbar in median only. The resulting changes in the diaphragm parameters when withdrawing the PEEP could be too small to be statistically significant with the small number of cases in this study. Another explanation for the missing difference might be the special characteristic of the cohort of patients in prolonged weaning which suffer from an extreme severe form of VIDD. Recent publications revealed that VIDD can be associated with a fibrotic remodelling of the diaphragm which already starts after few days of MV (49,50). It might be possible that a fibrotically remodelled diaphragmatic tissue has different properties in terms of flexibility, resulting in different patterns of its geometry after application of intrathoracic pressure. Further studies will be necessary to investigate this area in detail.

Despite there was paid utmost attention to keep image acquisition as uniform as possible, the acquired data show a wide statistical distribution also with in the examined individuals, which is not comprehensible at first sight. However, many aspects can influence the sonographic assessment. For instance, Tdi is highly dependent on location of the measurement, gender and patient position (51,52). But also the intraabdominal pressure and already small variations in the positioning of the ultrasound probe can cause relevant deviation with respect to the examined structure. This factor is particularly important in the examination of diaphragmatic excursion since the distance which the sound has to pass is very long and even a few degrees of deviation can lead to the examination of a completely different anatomic region. This constraint should be considered when assessing the diagnostic value of diaphragmatic ultrasound. Due to that fact, other researchers tackle this problem with the application of ortheses to keep the ultrasound probe consistently in a uniform position which markedly increased reliability (53).

Sonographic evaluation of the peripheral musculature

Intensive physiotherapeutic treatment is part of the structured weaning process and yields beneficial results (54,55). With improved mobilization, an increase in skeletal muscle diameter through training could consequently be expected. However, in the present study, we observed a decrease in the muscle cross-section of the quadriceps femoris over the entire weaning period. Possible explanations for this encompass massive fluid shifts with fluid overload and strong edema formation, especially in the extremities (56). Due to that, forced diuresis for negative fluid balancing is necessary during the weaning course. This muscular edema can cause the muscles to appear larger in diameter and become smaller as the treatment progresses and the negative balance increases. Nevertheless, it must be taken into account that a relevant proportion of patients in prolonged weaning suffer from a chronic critical illness which is associated with persistent protein catabolism and subsequent cachexia and muscle decay (57). It thus might be possible as well that the examined patients loose muscular mass due to catabolic processes which cannot be contained in full by physiotherapeutic measures. Moreover, recent studies showed that in the context of ICUAW, there are disturbances in the ability of peripheral muscles to regenerate, which further complicate muscle development (58). From a different perspective, however, it must also be noted that comprehensive active physiotherapeutic exercising with a focus on the peripheral muscles is not yet possible with insufficient respiratory muscles. It is therefore ultimately not possible to answer from the available data whether cellular mechanisms exist that allow the rehabilitation of peripheral muscles to proceed more slowly than that of the diaphragm muscles or whether insufficient exercise capacity of the muscles due to the insufficient respiratory system hinders the development of peripheral muscles. Although both diaphragmatic and peripheral muscles are classified as skeletal muscles, there is growing evidence that both muscle types are composed differently on a cellular level (18), which might also lead to a diverging behaviour when muscles have to be built up again. While a different behaviour between these two muscle groups is already shown for atrophy, data for rehabilitation is not available.

Strengths, limitations, and future research

Patients in prolonged weaning form a highly specialized patient population that exhibits a variety of characteristics, some of which are still poorly understood and researched. These characteristics also clearly distinguish weaning patients from patients who have been ventilated but only for a relatively short time. While there are several publications focusing on diaphragmatic ultrasound in weaning from MV, it must be emphasized that the majority of papers included patients undergoing MV for several days only. They are thus not comparable to the cohort of the present work. To the best of the authors' knowledge, the present study is the first one including exclusively patients from a highly specific cohort of prolonged weaning with a long-term duration of MV for sonographic assessment of the diaphragm.

However, there are limitations that need to be considered. The sample size of the present study is relatively small and acquired in a monocentric way. One reason for the drop-out of patients before completion of the weaning were external referrals to rehabilitation facilities. Additionally, it was aimed to examine a reliable sample of patients which are treated on the weaning unit. On the opposite, this led to a quite heterogeneous population with a strong predominance of patients after cardiac surgery. It must be acknowledged that the formation of more homogenous subgroups, which are composed by the pathogenesis of the respiratory failure, might also have yielded different results. For instance, the diaphragm of a patient with advanced chronic obstructive pulmonary disease (COPD), whose diaphragm already shows morphological changes due to years of chronic disease, might show a different behaviour in comparison to a patient with respiratory failure after a complicative surgery. The point that the cohort contained almost no patients that suffered weaning failure was not predictable, but nevertheless makes it difficult to generalise the results. Due to that fact, an analysis for possible cut-off values to predict weaning success or failure was not carried out. However, it must be critically questioned whether the available data, in the light of the pronounced scatter, permit application for a prognosis estimation at all.

In the end, the results of the present study deviate to some extent from previous publications, whose study cohorts however are not comparable. Further studies specifically with patients in prolonged weaning are necessary to reassess the results of the present work.

Two-dimensional sonographic parameters are only capable of reflecting the transversal changes of a muscle during contraction. The longitudinal, i.e., in the direction of contraction, is however of far bigger interest to monitor the contractility. Thus, an application of novel sonographic techniques, like the so-called speckle tracking sonography (36,59), which was derived from cardiac imaging and might be able to display the muscular activity better, is desirable in patients in prolonged weaning. Whether or not these techniques give a better insight into the alterations of diaphragms in severe VIDD will be up to further examination. It could also be that an isolated assessment of the diaphragm excludes other very important organs in prolonged weaning, namely the lung and the heart. It might be interesting to investigate whether a combined sonographic assessment of the lung, heart and diaphragm increases the clinical benefit of sonography in the treatment of patients with prolonged weaning, as it would be possible to detect, for example, cardiocirculatory problems that would be missed by an assessment of the diaphragm alone (42,60). Due to various confounders, the sonographic measurements of the peripheral muscle are difficult to interpret as well. Here, techniques that enable assessment of the individual fluid status and tissue composition like bioelectrical impedance analysis (61), might generate more reliable insights.

Conclusions

In conclusion, the present study has shown that the two-dimensional sonographic parameters of the diaphragm increased over the course of the weaning process. The influence of the application of MV on the sonographic parameters seemed to be limited. The peripheral musculature showed no increase over the time. In general, the results showed a high variability and further studies will be necessary to create more detailed insights into the heterogenous group of patients in prolonged weaning.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of the Faculty of Medicine, RWTH Aachen, Aachen, Germany (No. EK 402/19, 29.02.2020) and was registered at the German Clinical Trials Register (No. DRKS00020937). Written informed consent was taken from all individual participants or their health care proxy or legal guardian, if a patient was unable of giving consent himself/herself. As soon as independent consent by the patient was possible again at a later point in time, this was subsequently obtained. Study participation and data collection and could be stopped at any time at the explicit request of the patient or representative.

References

1. Kocjan J, Adamek M, Gzik-Zroska B, Czyżewski D, Rydel M. Network of breathing. Multifunctional role of the diaphragm: a review. Adv Respir Med 2017;85:224-32.
2. Ricoy J, Rodríguez-Núñez N, Álvarez-Dobaño JM, Toubes ME, Riveiro V, Valdés L. Diaphragmatic dysfunction. Pulmonology 2019;25:223-35.
3. Matamis D, Soilemezi E, Tsagourias M, Akoumianaki E, Dimassi S, Boroli F, Richard JC, Brochard L. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. Intensive Care Med 2013;39:801-10.
4. Zambon M, Greco M, Bocchino S, Cabrini L, Beccaria PF, Zangrillo A. Assessment of diaphragmatic dysfunction in the critically ill patient with ultrasound: a systematic review. Intensive Care Med 2017;43:29-38.

5. Umbrello M, Formenti P. Ultrasonographic Assessment of Diaphragm Function in Critically Ill Subjects. Respir Care 2016;61:542-55.
6. Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, Matecki S, Duguet A, Similowski T, Jaber S. Diaphragm dysfunction on admission to the intensive care unit. Prevalence, risk factors, and prognostic impact-a prospective study. Am J Respir Crit Care Med 2013;188:213-9.
7. Peñuelas O, Keough E, López-Rodríguez L, Carriedo D, Gonçalves G, Barreiro E, Lorente JÁ. Ventilator-induced diaphragm dysfunction: translational mechanisms lead to therapeutical alternatives in the critically ill. Intensive Care Med Exp 2019;7:48.
8. Hermans G, Agten A, Testelmans D, Decramer M, Gayan-Ramirez G. Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. Crit Care 2010;14:R127.
9. Supinski GS, Callahan LA. Diaphragm weakness in mechanically ventilated critically ill patients. Crit Care 2013;17:R120.
10. Pu L, Zhu B, Jiang L, Du B, Zhu X, Li A, Li G, He Z, Chen W, Ma P, Jia J, Xu Y, Zhou J, Qin L, Zhan Q, Li W, Jiang Q, Wang M, Lou R, Xi X. Weaning critically ill patients from mechanical ventilation: A prospective cohort study. J Crit Care 2015;30:862.e7-13.
11. Lu Z, Xu Q, Yuan Y, Zhang G, Guo F, Ge H. Diaphragmatic Dysfunction Is Characterized by Increased Duration of Mechanical Ventilation in Subjects With Prolonged Weaning. Respir Care 2016;61:1316-22.
12. Barchuk A, Barchuk SA, Roebken CK, Ahn J. Prevalence of Diaphragmatic Dysfunction in the Long-Term Acute Care Setting and Its Effects on Ventilator Weaning Outcomes: A Retrospective Cohort Study. Am J Phys Med Rehabil 2022;101:555-60.
13. Dres M, Dubé BP, Mayaux J, Delemazure J, Reuter D, Brochard L, Similowski T, Demoule A. Coexistence and Impact of Limb Muscle and Diaphragm Weakness at Time of Liberation from Mechanical Ventilation in Medical Intensive Care Unit Patients. Am J Respir Crit Care Med 2017;195:57-66.
14. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, Pearl R, Silverman H, Stanchina M, Vieillard-Baron A, Welte T. Weaning from mechanical ventilation. Eur Respir J 2007;29:1033-56.
15. Bornitz F, Ewert R, Knaak C, Magnet FS, Windisch W, Herth F. Weaning from Invasive Ventilation in Specialist Centers Following Primary Weaning Failure. Dtsch Arztebl Int 2020;117:205-10.
16. Davies MG, Quinnell TG, Oscroft NS, Clutterbuck SP, Shneerson JM, Smith IE. Hospital outcomes and long-term survival after referral to a specialized weaning unit. Br J Anaesth 2017;118:563-9.
17. Scheinhorn DJ, Hassenpflug MS, Votto JJ, Chao DC, Epstein SK, Doig GS, Knight EB, Petrak RA; Ventilation Outcomes Study Group. Post-ICU mechanical ventilation at 23 long-term care hospitals: a multicenter outcomes study. Chest 2007;131:85-93.
18. Meznaric M, Cvetko E. Size and Proportions of Slow-Twitch and Fast-Twitch Muscle Fibers in Human Costal Diaphragm. Biomed Res Int 2016;2016:5946520.
19. Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, Hopkins RO, Hough CL, Kress JP, Latronico N, Moss M, Needham DM, Rich MM, Stevens RD, Wilson KC, Winkelman C, Zochodne DW, Ali NA; ATS Committee on ICU-acquired Weakness in Adults; American Thoracic Society. An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. Am J Respir Crit Care Med 2014;190:1437-46.
20. Saccheri C, Morawiec E, Delemazure J, Mayaux J, Dubé BP, Similowski T, Demoule A, Dres M. ICU-acquired weakness, diaphragm dysfunction and long-term outcomes of critically ill patients. Ann Intensive Care 2020;10:1.
21. Wang W, Xu C, Ma X, Zhang X, Xie P. Intensive Care Unit-Acquired Weakness: A Review of Recent Progress With a Look Toward the Future. Front Med (Lausanne) 2020;7:559789.
22. Vanhorebeek I, Latronico N, Van den Berghe G. ICU-acquired weakness. Intensive Care Med 2020;46:637-53.
23. Carámbula A, Pereyra S, Barbato M, Angulo M. Combined Diaphragm and Limb Muscle Atrophy Is Associated With Increased Mortality in Mechanically Ventilated Patients: A Pilot Study. Arch Bronconeumol (Engl Ed) 2021;57:377-9.
24. Vivier E, Muller M, Putegnat JB, Steyer J, Barrau S, Boissier F, Bourdin G, Mekontso-Dessap A, Levrat A, Pommier C, Thille AW. Inability of Diaphragm Ultrasound to Predict Extubation Failure: A Multicenter Study. Chest 2019;155:1131-9.
25. Farghaly S, Hasan AA. Diaphragm ultrasound as a new method to predict extubation outcome in mechanically ventilated patients. Aust Crit Care 2017;30:37-43.
26. Li S, Chen Z, Yan W. Application of bedside ultrasound in predicting the outcome of weaning from mechanical ventilation in elderly patients. BMC Pulm Med 2021;21:217.

27. Yoo JW, Lee SJ, Lee JD, Kim HC. Comparison of clinical utility between diaphragm excursion and thickening change using ultrasonography to predict extubation success. Korean J Intern Med 2018;33:331-9.
28. Liu Y, Chen W. A SAS macro for testing differences among three or more independent groups using Kruskal-Wallis and Nemenyi tests. J Huazhong Univ Sci Technolog Med Sci 2012;32:130-4.
29. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. Thorax 2014;69:423-7.
30. Ferrari G, De Filippi G, Elia F, Panero F, Volpicelli G, Aprà F. Diaphragm ultrasound as a new index of discontinuation from mechanical ventilation. Crit Ultrasound J 2014;6:8.
31. Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, Brochard LJ, Bolz SS, Rubenfeld GD, Kavanagh BP, Ferguson ND. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med 2015;41:642-9.
32. Vivier E, Mekontso Dessap A, Dimassi S, Vargas F, Lyazidi A, Thille AW, Brochard L. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. Intensive Care Med 2012;38:796-803.
33. Spadaro S, Grasso S, Mauri T, Dalla Corte F, Alvisi V, Ragazzi R, Cricca V, Biondi G, Di Mussi R, Marangoni E, Volta CA. Can diaphragmatic ultrasonography performed during the T-tube trial predict weaning failure? The role of diaphragmatic rapid shallow breathing index. Crit Care 2016;20:305.
34. Banerjee A, Mehrotra G. Comparison of Lung Ultrasound-based Weaning Indices with Rapid Shallow Breathing Index: Are They Helpful? Indian J Crit Care Med 2018;22:435-40.
35. Holtzhausen S, Unger M, Lupton-Smith A, Hanekom S. An investigation into the use of ultrasound as a surrogate measure of diaphragm function. Heart Lung 2018;47:418-24.
36. Oppersma E, Hatam N, Doorduin J, van der Hoeven JG, Marx G, Goetzenich A, Fritsch S, Heunks LMA, Bruells CS. Functional assessment of the diaphragm by speckle tracking ultrasound during inspiratory loading. J Appl Physiol (1985) 2017;123:1063-70.
37. Rittayamai N, Hemvimon S, Chierakul N. The evolution of diaphragm activity and function determined by ultrasound during spontaneous breathing trials. J Crit Care 2019;51:133-8.
38. Llamas-Álvarez AM, Tenza-Lozano EM, Latour-Pérez J. Diaphragm and Lung Ultrasound to Predict Weaning Outcome: Systematic Review and Meta-Analysis. Chest 2017;152:1140-50.
39. Le Neindre A, Philippart F, Luperto M, Wormser J, Morel-Sapene J, Aho SL, Mongodi S, Mojoli F, Bouhemad B. Diagnostic accuracy of diaphragm ultrasound to predict weaning outcome: A systematic review and meta-analysis. Int J Nurs Stud 2021;117:103890.
40. Parada-Gereda HM, Tibaduiza AL, Rico-Mendoza A, Molano-Franco D, Nieto VH, Arias-Ortiz WA, Perez-Terán P, Masclans JR. Effectiveness of diaphragmatic ultrasound as a predictor of successful weaning from mechanical ventilation: a systematic review and meta-analysis. Crit Care 2023;27:174.
41. Li C, Li X, Han H, Cui H, Wang G, Wang Z. Diaphragmatic ultrasonography for predicting ventilator weaning: A meta-analysis. Medicine (Baltimore) 2018;97:e10968.
42. Haaksma ME, Smit JM, Heldeweg M, Nooitgedacht JS, Atmowihardjo LN, Jonkman AH, de Vries HJ, Lim EH, Steenvoorden T, Lust E, Girbes AR, Heunks LM, Tuinman PR. Holistic Ultrasound to Predict Extubation Failure in Clinical Practice. Respir Care 2021;66:994-1003.
43. Poulard T, Bachasson D, Fossé Q, Niérat MC, Hogrel JY, Demoule A, Gennisson JL, Dres M. Poor Correlation between Diaphragm Thickening Fraction and Transdiaphragmatic Pressure in Mechanically Ventilated Patients and Healthy Subjects. Anesthesiology 2022;136:162-75.
44. Vetrugno L, Orso D, Corradi F, Zani G, Spadaro S, Meroi F, et al. Diaphragm ultrasound evaluation during weaning from mechanical ventilation in COVID-19 patients: a pragmatic, cross-section, multicenter study. Respir Res 2022;23:210.
45. Jansen D, Jonkman AH, Vries HJ, Wennen M, Elshof J, Hoofs MA, van den Berg M, Man AME, Keijzer C, Scheffer GJ, van der Hoeven JG, Girbes A, Tuinman PR, Marcus JT, Ottenheijm CAC, Heunks L. Positive end-expiratory pressure affects geometry and function of the human diaphragm. J Appl Physiol (1985) 2021;131:1328-39.
46. Formenti P, Miori S, Galimberti A, Umbrello M. The Effects of Positive End Expiratory Pressure and Lung Volume on Diaphragm Thickness and Thickening. Diagnostics (Basel) 2023;13:1157.

47. Ali ER, Mohamad AM. Diaphragm ultrasound as a new functional and morphological index of outcome, prognosis and discontinuation from mechanical ventilation in critically ill patients and evaluating the possible protective indices against VIDD. Egypt J Chest Dis Tuberc 2017;66:339-51.
48. Hatam N, Goetzenich A, Rossaint R, Karfis I, Bickenbach J, Autschbach R, Marx G, Bruells CS. A novel application for assessing diaphragmatic function by ultrasonic deformation analysis in noninvasively ventilated healthy young adults. Ultraschall Med 2014;35:540-6.
49. Qian X, Jiang Y, Jia J, Shen W, Ding Y, He Y, Xu P, Pan Q, Xu Y, Ge H. PEEP application during mechanical ventilation contributes to fibrosis in the diaphragm. Respir Res 2023;24:46.
50. Shi Z, van den Berg M, Bogaards S, Conijn S, Paul M, Beishuizen A, Heunks L, Ottenheijm CAC. Replacement Fibrosis in the Diaphragm of Mechanically Ventilated Critically Ill Patients. Am J Respir Crit Care Med 2023;207:351-4.
51. Haaksma ME, van Tienhoven AJ, Smit JM, Heldeweg MLA, Lissenberg-Witte BI, Wennen M, Jonkman A, Girbes ARJ, Heunks L, Tuinman PR. Anatomical Variation in Diaphragm Thickness Assessed with Ultrasound in Healthy Volunteers. Ultrasound Med Biol 2022;48:1833-9.
52. Tuinman PR, Jonkman AH, Dres M, Shi ZH, Goligher EC, Goffi A, de Korte C, Demoule A, Heunks L. Respiratory muscle ultrasonography: methodology, basic and advanced principles and clinical applications in ICU and ED patients-a narrative review. Intensive Care Med 2020;46:594-605.
53. Molina-Hernández N, Chicharro JL, Becerro-de-Bengoa-Vallejo R, Losa-Iglesias ME, Rodríguez-Sanz D, Vicente-Campos D, Marugán-Rubio D, Gutiérrez-Torre SE, Calvo-Lobo C. Ultrasonographic reliability and repeatability of simultaneous bilateral assessment of diaphragm muscle thickness during normal breathing. Quant Imaging Med Surg 2023;13:6656-67.
54. Lippi L, de Sire A, D'Abrosca F, Polla B, Marotta N, Castello LM, Ammendolia A, Molinari C, Invernizzi M. Efficacy of Physiotherapy Interventions on Weaning in Mechanically Ventilated Critically Ill Patients: A Systematic Review and Meta-Analysis. Front Med (Lausanne) 2022;9:889218.
55. Bickenbach J, Fritsch S, Cosler S, Simon Y, Dreher M, Theisen S, Kao J, Hildebrand F, Marx G, Simon TP. Effects of structured protocolized physical therapy on the duration of mechanical ventilation in patients with prolonged weaning. J Crit Care 2024;80:154491.
56. O'Connor ME, Prowle JR. Fluid Overload. Crit Care Clin 2015;31:803-21.
57. Hawkins RB, Raymond SL, Stortz JA, Horiguchi H, Brakenridge SC, Gardner A, Efron PA, Bihorac A, Segal M, Moore FA, Moldawer LL. Chronic Critical Illness and the Persistent Inflammation, Immunosuppression, and Catabolism Syndrome. Front Immunol 2018;9:1511.
58. Batt J, Herridge MS, Dos Santos CC. From skeletal muscle weakness to functional outcomes following critical illness: a translational biology perspective. Thorax 2019;74:1091-8.
59. Fritsch SJ, Hatam N, Goetzenich A, Marx G, Autschbach R, Heunks L, Bickenbach J, Bruells CS. Speckle tracking ultrasonography as a new tool to assess diaphragmatic function: a feasibility study. Ultrasonography 2022;41:403-15.
60. Mousa A, Klompmaker P, Tuinman PR. Setting positive end-expiratory pressure: lung and diaphragm ultrasound. Curr Opin Crit Care 2024;30:53-60.
61. Dewitte A, Carles P, Joannès-Boyau O, Fleureau C, Roze H, Combe C, Ouattara A. Bioelectrical impedance spectroscopy to estimate fluid balance in critically ill patients. J Clin Monit Comput 2016;30:227-33.

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Supplementary

Table S1 Respirator settings and respiratory parameters at beginning and at end of weaning process

Parameter	First measurement	Last measurement
Ventilation mode		
Pressure controlled (Bilevel)	3 (6)	0
Assisted spontaneous breathing	47 (94)	50 (100)
Respiration rate (/min)	19 (8)	17.5 (10.5)
FiO_2	0.35 (0.15)	0.3 (0.05)
PEEP (mbar)	6 (1)	6 (2)
pInsp (mbar)	19 (N/A)	N/A
pASB (mbar)	10 (4)	10 (2)
Tidal volume (mL)	537.5 (230)	548.5 (302.5)
Respiratory minute volume (L/min)	10.2 (2.9)	8.85 (3.95)
Respiratory free time within the last 24 hours (min)	180 (360)	900 (210)

Data are given as median (IQR) or n (%). FiO_2, fraction of inspired oxygen; PEEP, positive end expiratory pressure; pInsp, inspiratory pressure; pASB, inspiratory assist pressure.

Table S2 Sonographic parameters over the first three measurements at beginning of weaning process

Sonographic parameter	Day 0 (at admission)		Day 3 after admission		Day 6 after admission		P value
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
Inspiratory diaphragmatic thickness (mm)	45	2.58 (1.64)	45	3.33 (1.33)	45	3.54 (1.47)	0.016
Expiratory diaphragmatic thickness (mm)	45	2.19 (1.34)	45	2.67 (1.25)	45	2.88 (1.21)	0.090
Fractional thickening (%)	45	15.03 (16.14)	45	13.66 (19.59)	45	18.42 (14.77)	0.033
Excursion (cm)	41	0.7 (0.6)	43	0.7 (0.7)	42	0.75 (0.7)	0.056
M. quadr. fem. (half) (cm)	45	1.6 (0.88)	45	1.7 (0.69)	45	1.58 (0.6)	0.249
M. quadr. fem. (lower third) (cm)	45	1.28 (0.46)	45	1.25 (0.63)	45	1.28 (0.39)	0.572

Data are given as median (IQR). The data consists of the averaged data with and without respirator at a given time point. The presence of a statistically significant difference over the course of time was examined using a Friedman rank sum test. Significance level α=0.05. IQR, interquartile range; M. quadr. fem., musculus quadriceps femoris.

Table S3 Pairwise comparisons of the parameter "Inspiratory diaphragmatic thickness"

Timepoint of measurement	Day 0 (at admission)	Day 3 after admission
Day 3 after admission	0.094	–
Day 6 after admission	0.004	0.49

Data represent the respective P values. Pairwise comparisons were carried out using a Wilcoxon-Nemenyi-McDonald-Thompson test. Significance level α=0.05.

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Table S4 Pairwise comparisons of the parameter "Fractional thickening"

Timepoint of measurement	Day 0 (at admission)	Day 3 after admission
Day 3 after admission	0.988	–
Day 6 after admission	0.439	0.355

Data represent the respective P values. Pairwise comparisons were carried out using a Wilcoxon-Nemenyi-McDonald-Thompson test. Significance level α=0.05.

Table S5 Sonographic parameters over the last three measurements before completion of weaning process.

Sonographic parameter	6 days before last measurement		3 days before last measurement		Last measurement before completion of weaning		P value
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
Inspiratory diaphragmatic thickness (mm)	45	3.30 (1.24)	45	2.88 (1.42)	45	2.72 (1.92)	0.186
Expiratory diaphragmatic thickness (mm)	45	2.64 (0.98)	45	2.48 (1.04)	45	2.32 (1.80)	0.077
Fractional thickening (%)	45	19.35 (16.75)	45	16.52 (11.33)	45	17.96 (11.99)	0.062
Excursion (cm)	42	0.75 (0.75)	43	0.75 (0.8)	42	0.88 (0.55)	0.029
M. quadr. fem. (half) (cm)	45	1.52 (0.59)	45	1.61 (0.62)	45	1.52 (0.53)	0.661
M. quadr. fem. (lower third) (cm)	45	1.23 (0.53)	45	1.23 (0.44)	45	1.27 (0.35)	0.979

Data are given as median (IQR). The data consists of the averaged data with and without respirator at a given time point. The presence of a statistically significant difference over the course of time was examined using a Friedman rank sum test. Significance level α=0.05. IQR, interquartile range; M. quadr. fem., musculus quadriceps femoris.

Table S6 Pairwise comparisons of the parameter "Excursion"

Timepoint of measurement	6 days before last measurement	3 days before last measurement
3 days before last measurement	0.581	–
Last measurement before completion of weaning	0.270	0.842

Data represent the respective P values. Pairwise comparisons were carried out using a Wilcoxon-Nemenyi-McDonald-Thompson test. Significance level α=0.05.

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