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Progressive Diaphragm Atrophy in Pediatric Acute Respiratory Failure

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Abstract

Objective—Diaphragm atrophy is associated with delayed weaning from mechanical ventilation (MV) and increased mortality in critically ill adults. We sought to test for the presence of diaphragm atrophy in children with acute respiratory failure (ARF).

Design—Prospective, observational study

Setting—Single-center tertiary non-cardiac PICU in a children's hospital

Patients—Invasively ventilated children with ARF

Measurements and Main Results—Diaphragm thickness at end-expiration (Tdi-exp) and end-inspiration (Tdi-insp) were serially measured by ultrasound in 56 patients (median age 17 months, IQR, 5.5–52), first within 36 hours of intubation and last preceding extubation. The median duration of MV was 140 hours (IQR, 83–201). At initial measurement, Tdi-exp was 2.0 mm (IQR, 1.8–2.5) and Tdi-insp was 2.5 mm (IQR, 2–2.8). The change in Tdi-exp during MV between first and last measurement was −13.8% (IQR, −27.4% to 0%), with a −3.4% daily atrophy

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Location of Study

Children's Hospital of Philadelphia, Philadelphia, PA

Reprints

No reprints will be ordered.

Conflicts of Interest

The authors have no conflicts of interest to report related to the content of this manuscript. Christie Glau, Thomas Conlon, Adam Himebauch and Akira Nishisaki have received honoraria and travel reimbursement from the Society of Critical Care Medicine.

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rate (IQR, −5.6 to 0%). Thickening fraction [TF = (Tdi-insp – Tdi-exp)/Tdi-insp] throughout the course of MV was linearly correlated with spontaneous breathing fraction (SBF) (beta coefficient 9.4, 95% CI 4.2, 14.7, p=0.001). For children with a period of SBF < 0.5 during MV, those with exposure to a continuous neuromuscular blockade (NMB) infusion (n=15) had a significantly larger decrease in Tdi-exp compared to children with low SBF who were not exposed to a NMB infusion (n=18) [−16.4%, (IQR, −28.4% to −7.0%) versus −7.3%, (IQR, −10.9% to −0%); p=0.036].

Conclusions—Diaphragm atrophy is present in children on MV for ARF. Diaphragm contractility, measured as TF, is strongly correlated with SBF. The combination of exposure to NMB infusion with low overall SBF is associated with a greater degree of atrophy.

Keywords

Ultrasound; Diaphragm; Diaphragm Atrophy; Acute Respiratory Failure; Ventilator Induced Diaphragm Dysfunction; Ventilation; Mechanical

Introduction

An estimated 30% of children admitted to pediatric ICUs (PICU) in the United States require mechanical ventilation (MV) for a median of 5–6 days.[1] Substantial evidence within adult critical care literature supports the existence of ventilator induced diaphragmatic dysfunction (VIDD), defined as a MV-induced loss of diaphragmatic force-generating capacity characterized by muscle fiber atrophy, myofibril necrosis and disorganization.[2–4] Diaphragm atrophy occurs within as few as 18 hours of MV[5], progresses at a rate between 4–7% per day of MV[6–8] and is associated with extubation failure and increased mortality.[9, 10] The progression of diaphragm atrophy is exacerbated by the length of MV, low spontaneous breathing fraction (SBF), use of neuromuscular blockade (NMB) and exposure to corticosteroids.[11] Although diaphragmatic contraction is integral to the generation of inspiratory force[12] in children with immature chest wall musculature, there are limited data on VIDD in pediatric acute respiratory failure (ARF).

Diaphragm contractility can be assessed by measurement of diaphragm thickening during inspiration and expressed as a thickening fraction (TF).[13–15] Diaphragm TF correlates strongly with diaphragm strength when assessed against reference measurements of negative intrathoracic pressure in response to phrenic nerve stimulation.[16] Diaphragm atrophy and associated diminished TF[17] have been associated with delayed liberation from MV with the duration of intubation being directly correlated to the level of inspiratory effort.[18] Therefore, diaphragmatic atrophy and resultant dysfunction are likely to be a *modifiable* risk factors in the outcome in pediatric ARF.

Bedside ultrasound (US) is a non-invasive method to interrogate the size and contractility of the diaphragm at its insertion site with the chest wall (the zone of apposition). Contraction in this region drives the inspiratory pressure-volume work relationship and is directly proportional to inspiratory force.[19–21] To address the lack of pediatric data, we sought to test the hypothesis that diaphragm atrophy occurs in pediatric acute respiratory failure at a daily rate similar to that seen in adults undergoing MV based on non-invasive US

measurements. We also evaluated the correlation between TF and SBF and the association of exposure to continuous NMB infusion and exposure to corticosteroids with diaphragm atrophy during low spontaneous respiratory effort (SBF < 0.5).

Materials and Methods

Setting/Population

This study was conducted in an academic, non-cardiac, 55 bed PICU in the United States. The study was approved by the Institutional Review Board and informed consent was obtained from each subject's legal guardian. A convenience sample of subjects < 18 years old who required invasive MV for > 24 hours were enrolled between January 2016 and April 2017. Included subjects were endotracheally intubated and mechanically ventilated with clinician intent to continue MV for greater than 24 hours. Subjects with pre-existing diagnoses of neuromuscular weakness, diaphragm paresis, chronic respiratory failure with ongoing requirement for invasive MV or continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) or with likely death within 48 hours were excluded.

Study design

Enrolled subjects underwent diaphragm measurements by US within 36 hours of initiation of MV. Measurements were repeated 48–72 hours after the initiation of MV, after one week of MV and weekly thereafter for the duration of MV. Evaluable subjects were those who had two or more measurements performed during the course of MV. Demographic information, including age, sex, height, weight, primary ICU admission diagnosis and comorbid conditions, was recorded. Exposure to and duration of continuous NMB infusion during the course of MV (exclusive of intermittent NMB dosing) and use of corticosteroids were recorded. Ventilator logs were interrogated at the time of each US measurement to ascertain the mode of ventilation, ventilator settings and SBF (the proportion of breaths initiated by the subject during MV) for the 24 hours preceding each US measurement. Extubation success, defined as no requirement for re-intubation within the 48 hours following extubation, and requirement for non-invasive ventilation (CPAP or BiPAP) following extubation were recorded.

Ultrasound Measurements

All US measurements were performed with the SonoSite M-Turbo® (FUJIFILM SonoSite, Inc., Bothell, Washington) using the L12-4 MHz Linear Array Transducer. Subjects were imaged in a semi-recumbent position with the head of bed at a 30-degree angle. Measurements were made of the right hemidiaphragm since the feasibility and repeatability of right hemidiaphragm measurements are superior to those of the left hemidiaphragm in the adult literature[21] and no significant difference between diaphragm thickness (Tdi) or TF has been demonstrated between the left and right hemidiaphragms.[8, 20, 21] The transducer was positioned in the coronal plane in the mid-axillary line in the zone of apposition between the 9th and 10th intercostal space as first described by Cohn *et al.*[22] and replicated by others.[6, 21, 23, 24] At this position, B-mode US was utilized to measure resting Tdi at end-expiration (Tdi-exp) and end-inspiration (Tdi-insp). Tdi-insp was measured during a spontaneous breath for subjects who were capable of spontaneous triggering and during a

controlled breath for those who were not spontaneously breathing. Diaphragm thickness was defined as the outer edge of the peritoneal membrane to the outer edge of the diaphragmatic pleura (Figure 1). In this same position, M-Mode (motion mode) ultrasonography was used to measure Tdi-insp and Tdi-exp in order to ascertain diaphragm TF (Figure 2). The mean value of three separate measurements was used for analysis. All measurements in the study were performed by a single pediatric intensivist (CG) who is credentialed to perform bedside US. A second pediatric intensivist (TC) repeated ultrasound imaging on 4 subjects on 8 separate occasions coinciding with the timing of the primary ultrasonographer's scans. The interrater reliability correlation coefficient for diaphragm thickness measurements was 0.94 (p=0.0003) for repeated ultrasound imaging and measurements by a second provider. Treating clinicians were blinded to the results of the diaphragm measurements and respiratory data, thus no clinical decisions were made based on the data collected as part of this study.

Statistical analysis

The sample size calculation was derived from adult literature reporting a baseline diaphragm size of 2.0–3.0 mm (SD 0.5–1 mm) and daily atrophy rate of 6% during MV.[6] We estimated a resting end-expiratory pediatric diaphragm thickness of 2.2 mm with SD 0.5 mm and estimated the range of possible percent change in diaphragm thickness to be between (−30 to −9%) given the estimated median length of intubation of 5–6 days.[1] A total of 52 evaluable subjects would be required to detect the lower percent estimated change of −9%. Summary statistics were described with mean and SD for parametric variables and mean with interquartile range (IQR) for nonparametric variables. The change of Tdi during MV was calculated as follows: [Tdi-exp (last measurement prior to extubation) – Tdi-exp (initial measurement after intubation)] / Tdi-exp (initial measurement after intubation)]. Resting diaphragm thickness at end-expiration (Tdi-exp) was used for diaphragm atrophy calculations since inspiratory diaphragm thickness is affected by inspiratory effort. The change of Tdi during periods when spontaneous breaths were less than 50% of delivered breaths (SBF<0.5) was calculated as follows: [Tdi-exp (last measurement during MV with SBF<0.5) – Tdi-exp (initial measurement after intubation)] / Tdi-exp (initial measurement after intubation)]. Diaphragm thickening fraction (TF) was calculated at each time point using the following formula: TF = (Tdi-insp – Tdi-exp)/Tdi-insp. Wilcoxon sign-rank test was used to assess the subjects' longitudinal Tdi-exp change, and Wilcoxon rank-sum test was used to compare two independent groups. Association between TF and SBF was assessed using linear regression after inspection of data with a two-way scatter plot. Variance was adjusted for clustering within subjects. STATA® 14.0 (College Station TX, USA) was used and a p-value<0.05 was considered statistically significant.

Results

A total of 56 subjects were enrolled. Fifty-two subjects had 2 or more diaphragm measurements allowing for atrophy analyses (four subjects were extubated prior to final diaphragm measurements being performed). Demographics for enrolled subjects are shown in Table 1. The median length of MV was 140 hours (IQR, 83–201). Extubation failure occurred in 2/56 (3.6%), and 25/56 (44.6%) required non-invasive ventilation (CPAP or

BiPAP) during the 24 hours following extubation. The initial diaphragm measurement was done at median 19 hours (IQR, 11.5–28) after intubation, and the final diaphragm measurement was done at median 5 hours (IQR, 2–27) prior to extubation.

Assessment of diaphragm atrophy

The initial median Tdi-exp was 2.0 mm (IQR, 1.8 to 2.5), Tdi-insp 2.2 mm (IQR, 2.0 to 2.7). The median percentage change in Tdi-exp over the total duration of MV (between initial and final Tdi-exp measurements) was −13.8% (IQR, −27.4 to 0) with a daily rate of atrophy of −3.4% per day of MV (IQR, −5.6 to 0) (Figure 3).

Assessment of diaphragm thickening fraction

The median diaphragm TF at the initial measurement was 9.7% (IQR, 6.5 to 16.4) and within 24 hours prior to extubation was 14.8% (IQR, 10.9 to 26.8, n=38). Throughout the course of MV, diaphragm TF was found to be significantly correlated with SBF during the 24 hours preceding each diaphragm measurement (beta coefficient = 9.4, 95% CI 4.2–14.7, p=0.001; Figure 4).

Assessment of diaphragm atrophy and exposure to neuromuscular blockade

Nineteen subjects received continuous NMB infusion during the study period with median duration of NMB infusion of 68 hours (IQR, 35 to 98). Subjects exposed to NMB had a longer median length of MV than those not exposed to NMB [158 hours (IQR, 121 to 245) vs. 117 hours (IQR, 80 to 182), p=0.019]. There was a trend toward increased daily rates of atrophy among subjects exposed to NMB [−5.2%, (IQR, −14.8 to −1.9)] when compared to unexposed patients [−3.0%, (IQR, −5.1 to 0), p=0.065]. The proportion of change in Tdi-exp over the entire duration of MV was not different among subjects receiving continuous NMB infusions versus those without continuous NMB infusion exposure [−19.3%, (IQR, −32.7 to −6.7) vs. −8.5%, (IQR, −21.3 to 0), p=0.14].

Assessment of diaphragm atrophy and exposure to corticosteroids

Thirty-seven subjects received systemic corticosteroids during MV. There was no significant difference in the daily rate of atrophy among subjects exposed to corticosteroids [−3.8%, (IQR, −6.8 to −0.9)] when compared to unexposed patients [−1.8%, (IQR, −5.1 to 1.8), p=0.11]. There was a trend toward a greater degree of atrophy as measured by change in Tdi-exp over the entire duration of MV in subjects who received systemic corticosteroids compared to subjects who did not receive corticosteroids [−19%, (IQR, −31.3 to −6.5) versus −3.7%, (IQR, −18.4 to 3.5), p=0.096].

Diaphragm measurements and correlations during SBF<0.5

Thirty-three subjects had more than one measurement performed during a period of low spontaneous respiratory effort (SBF<0.5). The median duration of SBF<0.5 among these subjects was 51 hours (IQR, 42–147). The median change in Tdi-exp was −9.0% (IQR, −19.4 to −1.3) with a daily rate of atrophy of −3.9% (IQR, −7.4 to −0.2). For subjects with a period of SBF<0.5 during MV, subjects exposed to NMB infusion (n=15) had a significantly greater degree of diaphragm atrophy than subjects who were not exposed to NMB infusion

(n=18) [median Tdi-exp −16% (IQR, −28 to −7) vs. −7% (IQR, −11 to 0), p=0.036] (Figure 5). The diaphragm atrophy among subjects who received corticosteroid during SBF<0.5 was not significantly different when compared to the subjects who did not receive corticosteroids [corticosteroid group (n=22) median −12%, (IQR, −25 to −6) vs. non-corticosteroid group (n=11) −7%, (IQR, −19% to 3%), p=0.21].

Discussion

In this study, critically ill children with ARF of heterogeneous etiology demonstrated a 3.4% decrease in median diaphragm thickness per day of MV. Thickening fraction was significantly associated with SBF, indicating that the degree of spontaneous respiratory effort during MV is correlated with diaphragm contractility. Children exposed to NMB infusion demonstrated a trend toward higher daily rates of diaphragm atrophy when compared to children not exposed to NMB infusion. A trend toward greater overall diaphragm atrophy in those exposed to corticosteroids was observed when compared to children not exposed to corticosteroids during MV. When comparing subjects with low spontaneous breathing fraction (SBF <0.5), subjects with exposure to NMB infusion demonstrated a significantly greater degree of diaphragm atrophy than those with SBF <0.5 not exposed to NMB infusion.

The substantial daily rate of diaphragm atrophy (3.4%) demonstrated in this study cohort is consistent with adult literature. Zambon *et al* demonstrated a mean daily change in diaphragm thickness of −7.5% ±12.3 in critically ill adults undergoing controlled MV without pressure support (PS), −5.6% ± 12.9 for subjects in PS ventilation with PS > 12 cm H_20, and −1.5% ±10.9 for subjects in PS ventilation with PS 5–12 cm H_20.[8] In a multivariable analysis, use of low-levels of PS was found to be associated with less diaphragm atrophy, supporting a role for spontaneous ventilation modes that facilitate patient effort. Our study was not powered to detect daily atrophy rates for differing levels of respiratory support or determine whether the degree of PS was predictive of the daily rate of diaphragm atrophy. Nearly all of the enrolled subjects were successfully liberated from invasive mechanical ventilation which limited the ability to assess the clinical significance of diaphragm atrophy with regard to extubation success. Future studies should be performed to investigate the clinical impact of diaphragm atrophy in pediatric ARF. Considering the low rate of extubation failure (4–8%) in pediatric patients on MV for > 48 hours[25] this analysis could examine the association of diaphragm atrophy and duration of MV, ICU length of stay or requirement for non-invasive mechanical ventilatory support following extubation as clinically meaningful outcome metrics.

Our study demonstrated a strong correlation between SBF and diaphragm TF. Although diaphragm atrophy was demonstrated in this study cohort, the median TF at extubation was higher than the initial TF measurement. This could be explained by differences in sedation and NMB use in the initial phases of MV versus the peri-extubation period. The increase in TF prior to extubation could also reflect recovery of diaphragm function during MV weaning prior to clinician determination of extubation readiness. Diminished TF has been demonstrated with increased frequency in adult patients with difficultly weaning from MV. [26] Subjects with diaphragm TF maintained at similar levels to the TF of healthy patients

have been demonstrated to have shorter lengths of MV and ICU stay.[18] This suggests that mechanical ventilation strategies which maintain diaphragm contractility may facilitate weaning from mechanical ventilation. TF has also been examined as a potential marker of extubation readiness with TF > 36% predictive of a successful spontaneous breathing trial[15] and TF ≥ 30% with successful extubation.[10] These TF cutoff levels are substantially higher than the median TF (13.8%) within 24 hours prior to extubation in this current study, although nearly all (96%) were extubated successfully. This might be explained by nearly half of our patients being extubated to non-invasive mechanical ventilation. Alternatively, this might suggest that the TF threshold predictive of successful extubation may be different in the pediatric population. As diaphragm TF is dependent on patient effort, and within pediatric critical care a large proportion of patients require sedation to facilitate MV, further study is needed to establish normal TF values in children with spontaneous breathing on MV. Whether TF could be utilized as a tool to evaluate extubation readiness in children should be investigated.

During SBF<0.5, children exposed to NMB infusion displayed a larger magnitude of atrophy compared to children without exposure to NMB infusion. This suggests that NMB infusion can induce further diaphragm atrophy beyond that created from lack of spontaneous respiratory effort alone. Interestingly, when comparing the total change in Tdi-exp over the entire course of MV, subjects exposed to NMB infusion did not have significantly greater Tdi change than those who were not exposed to NMB infusion. Some of the subjects displayed an initial period of diaphragmatic atrophy followed by a recovery of diaphragm thickness during MV before extubation as shown in Figure 3. This could explain the lack of significant difference between these two groups when the diaphragm atrophy was calculated over the entire duration of MV and suggests a subset of patients in whom muscle atrophy can be reversed.

Our results suggested increased diaphragm atrophy among children who received corticosteroids compared to those who did not, though this did not reach statistical significance. Animal studies have shown mixed results when examining the association of corticosteroid administration with Tdi changes during MV.[27] Adult studies also did not demonstrate significant association between corticosteroid administration and diaphragmatic atrophy during MV.[17, 24] Given that our study was not powered to evaluate the effect of steroid exposure, and the difference between two groups was relatively large (−19.0% in corticosteroid group vs. −3.7% in non-exposure group), we believe the effect of corticosteroid exposure on pediatric diaphragm atrophy remains unknown, requiring future study to specifically address this concern.

The current study adds to current literature as the first to examine diaphragm atrophy during MV in the pediatric population and by demonstrating that Tdi and TF measurements are feasible and reproducible in children. The heterogeneity of subjects enrolled in the current study allow these results to be broadly generalizable, however further study should be conducted to determine the incidence and severity of diaphragm atrophy in specific disease populations.

The current study is limited by a small sample size which did not provide sufficient power to detect differences in study subgroups. Other limitations include patient heterogeneity, with lack of standardization of MV strategy, NMB and sedation as well as relatively short median duration of intubation indicating a likely low overall severity of illness in this cohort. Only two subjects failed extubation and many extubated to non-invasive mechanical ventilation; therefore, we were not able to make inferences about the association of diaphragm atrophy and TF with extubation success. The frequency of US measurements was affected by availability of the ultrasonographer, resulting in limited data points. The ability to perform frequent daily ultrasounds on enrolled subjects would have allowed for a richer exploration of diaphragm atrophy rates at varying levels of ventilator support. The study did not account for intermittent doses of NMB administered to patients in the group without exposure to NMB infusion, which could have led to a misclassification bias. No diaphragm measurements were performed following extubation, therefore the trajectory of change in diaphragm thickness following extubation could not be described. In existing adult literature, rapid recovery of diaphragm thickness and contractility has been observed.[9] Additional investigation into the recoverability of diaphragm atrophy in the pediatric population should be performed.

Conclusion

Progressive diaphragm atrophy occurs in pediatric ARF and is detectable by bedside ultrasound. Diaphragm TF was strongly correlated with SBF during MV. Exposure to NMB was associated with greater rate of diaphragm atrophy when SBF was low. Further study is necessary to explore the clinical implications of diaphragm atrophy in pediatric ARF.

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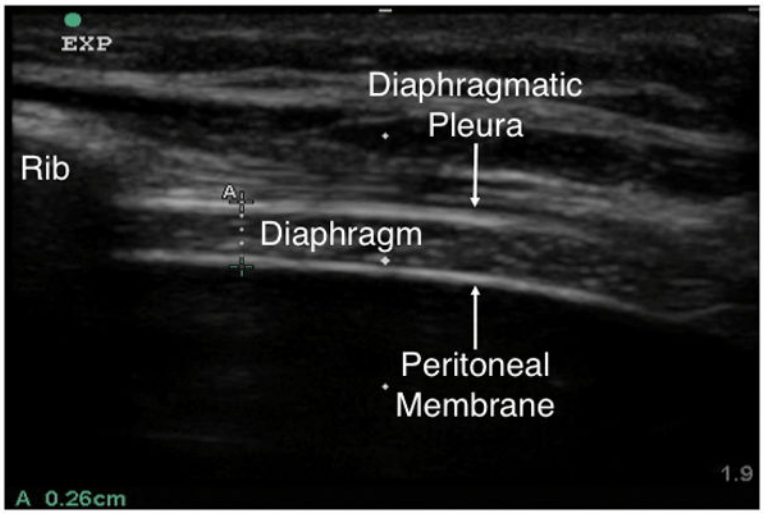

Figure 1.
B-Mode Ultrasound Measurement of Diaphragm Thickness at the Zone of Apposition at End-expiration.

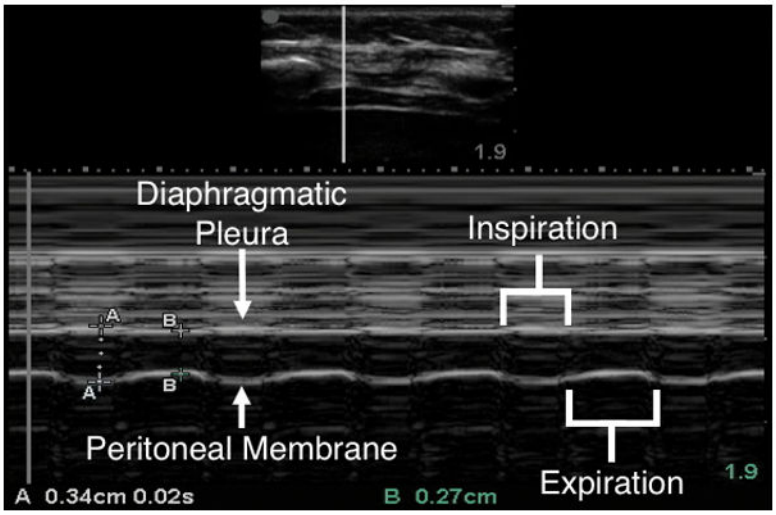

Figure 2.
M-mode Ultrasound Measurement of Diaphragm Thickening Fraction at the Zone of Apposition.

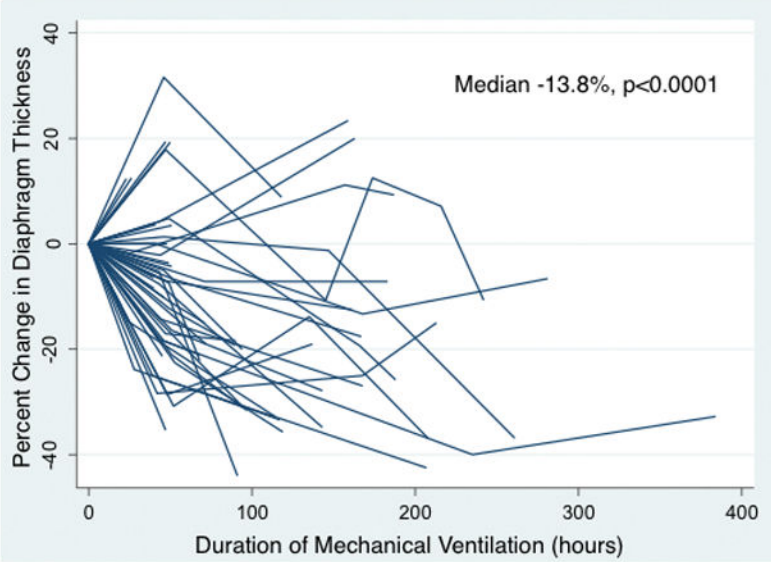

Figure 3.
Percentage Change in Diaphragm Thickness by Subject, n=52.

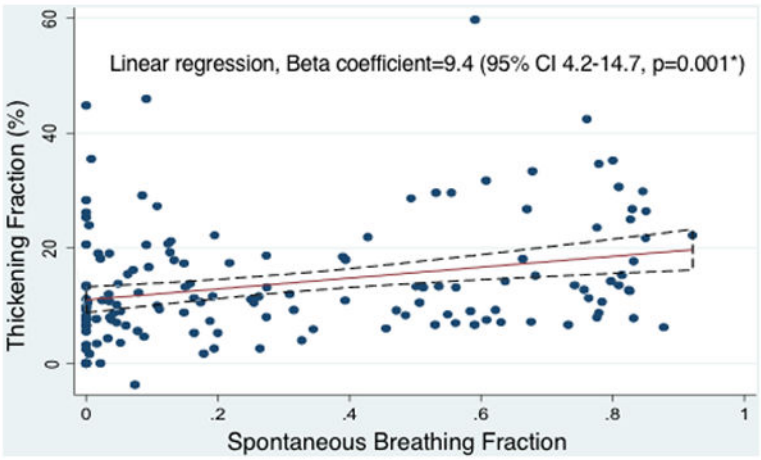

Figure 4.

Correlation of Diaphragm Thickening Fraction and Spontaneous Breathing Fraction. *P-value was adjusted for clustering by subject.

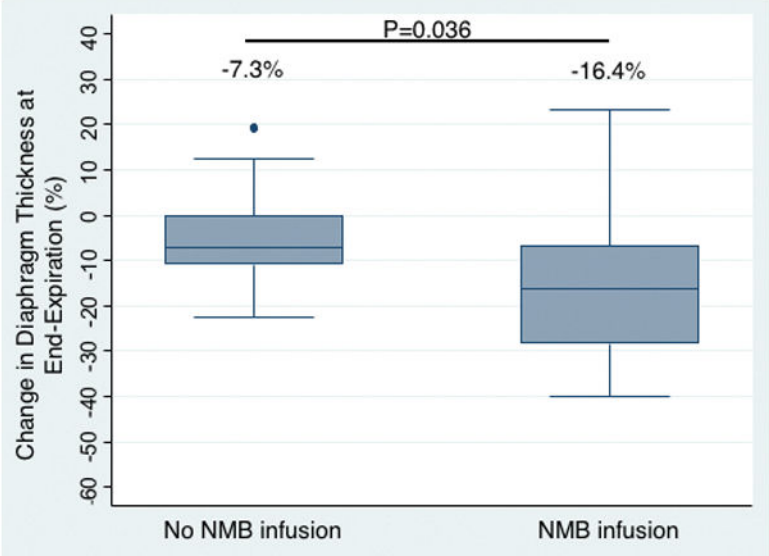

Figure 5.
Change in Diaphragm Thickness during Period of Mechanical Ventilation with Spontaneous Breathing Fraction < 0.5.

Table 1

Demographics.

***N* = 56**	**Median (IQR) or *n* (%)**
Age (months)	16.5 (5.5–52)
Sex	
Male	32 (57)
Female	24 (43)
Primary Reason for Endotracheal Intubation	
Bronchiolitis	20 (36)
Pneumonia	9 (16)
Upper Airway Obstruction	8 (14)
Septic Shock	5 (9)
Altered Mental Status	5 (9)
Status Asthmaticus	3 (5)
Aspiration	2 (4)
Post-operative	1 (2)
Subjects with Comorbidities	27 (48)
Duration of Mechanical Ventilation (hours)	140 (83–201)
Measurements per Subject	3 (2–3)
Subjects who Failed Extubation	2 (3.6)
Subjects who Received Neuromuscular Blockade Infusions	19 (34)
Subjects who Received Systemic Steroids	40 (71)
Initial Tdi-Exp (mm)	2.0 (1.8–2.5)
Initial Tdi-insp (mm)	2.2 (2.0–2.7)
Initial TF (%)	9.7 (6.5–16.4)

IQR= Interquartile Range, Tdi-Exp= Diaphragm thickness at end-expiration, Tdi-Insp= Diaphragm thickness at maximal inspiration, TF= Diaphragm thickening fraction