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DIAPHRAGMATIC THICKNESS ANALYSIS AS MARKER OF VENTILATOR INDUCED DIAPHRAGMATIC DYSFUNCTION IN MECHANICALLY VENTILATED CHILDREN : A PROSPECTIVE OBSERVATIONAL STUDY

Paediatrics

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ABSTRACT

Objective: To detect the occurrence of diaphragmatic dysfunction in the mechanically ventilated children by serial ultrasonographical measurement of the diaphragmatic thickness and calculation of daily atrophy percentage of diaphragmatic muscle mass. **Study Design:** In this hospital based descriptive type of observational study, conducted at the Pediatric intensive care unit of Department of Pediatrics, National Institute of Medical Science & Research Forty six children aged 1month to 18 years; who required invasive MV for more than 24 hours and did not meet exclusion criteria were enrolled. The patients underwent their first USG assessment of diaphragmatic thickness within twelve hours of intubation to obtain baseline measurements.Thereafter USG measurements were taken daily until the child was extubated, underwent tracheostomy or died. **Results:** Overall patients underwent a daily atrophy rate of 2.20%. The thickening fraction reduced from baseline of 22.47% to 19.53% pre-extubation. There was a significant recovery of both diaphragmatic muscle mass and diaphragmatic thickening fraction within 24 hours of extubation. No Differences were found in diaphragmatic indices in children ventilated for respiratory vs non respiratory causes. **Conclusions:** Use of diaphragmatic ultrasound to evaluate diaphragmatic function is both feasible and simple. There is a consistent pattern of ventilator induced diaphragmatic dysfunction (VIDD) occurring in the mechanically ventilated pediatric population, in terms of decreasing muscle mass and decreased thickening fraction of the diaphragm.

KEYWORDS

OBJECTIVE

Mechanical ventilation is an essential and frequently used tool in today's paediatric intensive care units. It is estimated that approximately one third of patients admitted in PICU require mechanical ventilation (MV) for a median of 4–6 days.[1,2] However, mechanical ventilation can be a double edged sword as recent evidence, especially within adult critical care literature supports the existence of ventilator induced diaphragmatic dysfunction (VIDD). VIDD has been defined as MV induced loss diaphragmatic force-generating capacity specifically related to the use of mechanical ventilation. The weakness cannot be readily explained by other factors such as sepsis, drugs, metabolic derangements, and so forth.[3,4,5] VIDD is pathologically characterized by muscle fiber atrophy, myofibril necrosis, and disorganization.[6,7] Multiple studies have validated USG guided assessment of diaphragm thickness as a reliable assessment of diaphragmatic function.[8–10]

USG is a non-invasive bedside alternative for assessment of diaphragmatic morphology and function.[11] It can assess the morphological changes by serial measurements of diaphragmatic thickness at end-expiration. Whereas the diaphragmatic thickening fraction is an indicator of diaphragmatic function, assessed as percentage change in diaphragmatic thickness between inspiration and expiration and can be expressed as DTF = [(TDi – TDe) X 100 / TDe].[3,12]

Weaning predictors such as rapid shallow breathing index, airway occlusion pressure 0.1 s, maximum inspiratory pressure and the weaning index have been used to improve the rate of successful weaning in adult studies. However, recent studies have shown that diaphragmatic ultrasound is still a better predictor of the outcome of weaning than the techniques mentioned above.[13] Data generated by this study can help assess the occurrence of VIDD in the pediatric population and may also be used to develop USG guided weaning predictors in children.

METHODS

This study was conducted in the Pediatric Intensive Care Unit of Department of Pediatric Medicine, National Institute of Medical Science & Research, Jaipur from July 2022 to December 2023. A convenience sample of forty six subjects aged 1month to 18 years who required invasive MV for more than 24 hours and did not meet exclusion criteria were enrolled. Included subjects were endotracheally intubated and mechanically ventilated with clinician intent to continue MV for more than 24 hours.

Children mechanically ventilated for more than 24 hours before PICU admission or died within 24 hours of admission were excluded. Children with pre-existing diagnoses of diaphragm paresis or neuromuscular weakness and children with chronic respiratory failure were also excluded. This study was prospective type of observational study.

After duly informed consent, demographic information including age, sex, height, weight, endotracheal tube size and primary PICU admission diagnosis were recorded. The patients underwent their first assessment of diaphragmatic thickness at end expiration (TDe), diaphragmatic thickness at end inspiration (TDi) within twelve hours of intubation to obtain baseline measurements. For prediction of diaphragmatic atrophy and dysfunction, information regarding daily ventilation details including mode of ventilation, tidal volume, PEEP, FiO2 and respiratory rate were recorded during each reading. All children were ventilated as per unit's existing disease specific ventilation and sedation protocols. The initial mode of ventilation was pressure regulated volume control with pressure support, and sedative and ventilatory setting were titrated to encourage spontaneous breathing. Thereafter measurements of TDi and TDe were taken daily until the child was extubated, underwent tracheostomy or died. The measurements were continued until 14 days in cases of prolonged ventilation. In case of extubation one measurement was taken between 12 to 24 hours after extubation. Need for re-intubation within 48 hours of extubation was classified as extubation failure. Clinical outcomes like hospital mortality, need for tracheostomy and duration of mechanical ventilation were documented.

The diaphragm thickness was measured using a Philips Sonosite machine with 8 - 10 MHz linear ultrasound probe. Measurements were made of the right hemidiaphragm since the feasibility and repeatability

of right hemidiaphragm measurements have been found superior in literature due to the liver being used as an echogenic window. Subjects were imaged in a semi-recumbent position with the head of bed at a 30-degree angle. The transducer was positioned perpendicular to the chest in the midaxillary line at the zone of apposition between the ninth and tenth intercostal space.In this area, the diaphragm is imaged as three-layer structure, including two parallel echoic lines (the diaphragmatic pleura and the peritoneal membrane) and a hypo-echoic structure between them (the muscle itself). On the frozen images, the distance from the middle of the pleural line to the middle of the peritoneal line was taken as the diaphragm thickness.

The diaphragm thickness measurement was taken three times on the same scan and the average value was calculated. At this position, B-mode US was utilized to measure resting TDe and TDi. TDi 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. In this same position, motion mode ultrasonography as used to measure TDi and TDe in order to ascertain diaphragm thickening fraction. The mean value of three separate measurements was used for analysis. All measurements in the study were performed by a single paediatric intensivist.

TDe represents the diaphragm at rest and is not influenced by level of sedation, and respiratory efforts. Hence, TDe was used as representative of diaphragmatic muscle bulk, and was used for diaphragmatic atrophy estimation. Diaphragmatic atrophy (%) was defined as percentage change in TDe over first 14 days, or completed days of ventilation if extubated/ died from baseline TDe as follows: [(baseline TDe – last TDe) X 100 / baseline TDe]. Diaphragmatic atrophy rate (% per day) was defined as average daily diaphragmatic atrophy as follows: [(baseline TDe – last TDe) X 100/ (days of ventilation X baseline TDe)]. Diaphragm thickening fraction (DTF) was calculated as follows DTF = [(TDi – TDe) X 100 / TDe]. The DTF for each patient was the mean of the values measured in three breaths.

Continuous data was described as mean (SD) for parametric data or median (IQR) for non-parametric data and categorical data was represented as absolute numbers and percentages. For continuous data, the Saphiro-Wilk test was performed to assess the normality and where appropriate the data was analyzed with required statistical tests and descriptive statistics. Degree of association of predictors of baseline DT and diaphragmatic atrophy rate were analyzed by Mann Whitney-U test and Spearman correlation co-efficient for categorical and continuous variables, respectively. As the Data was determined to be non-parametric it was analyzed by Mann-Whitney U test and Spearman correlation co-efficient. Likewise, Spearman co-efficient correlation test was used to find the association of diaphragmatic thickness fraction with demographic variables. Microsoft Word 2016 and Microsoft Excel 2016 were used for data recording and analysis. Data was analyzed using statistical software SPSS version 25.0. For all statistical tests, the p-value was taken less than 0.05 to indicate the valid evidence for statistical significance of the data.

Clearance from Departmental Ethics Committee was taken prior to the start of the study. All participants had the option to withdraw from the study anytime during their hospital stay.

RESULTS

In this prospective observational study, a total of 50 pediatric patients who were intubated and mechanically ventilated were assessed, of these 46 patients were finally enrolled. Out of 46 children maximum of the study participants were in the age group of 11-17 years (34.8%). The mean age of the study participants was observed to be 7.2±5.5 years. Majority of the study participants were males (63%), while 37% of them were females. Male to Female ratio was 2:1 in this study. We looked for indications of intubation among the study participants, which showed the most common being respiratory (39.1%), followed by cardiac (30.4%) and neurological (26.1%).

A notable portion of study participants (28.3%) experienced death. In contrast, a substantial number (30.4%) were successfully extubated and transitioned to non-invasive ventilation (NIV), demonstrating a positive response to treatment. Additionally, 34.8% were extubated to oxygen or room air (RA), suggesting that a significant proportion of participants could be weaned off from mechanical ventilation. Only one participant (2.2%) required. Finally, 4.3% of participants underwent tracheostomy, which is indicative of chronicity of illness in severe cases.

The mean baseline TDi value was 2.09 mm with a standard deviation of 0.25 mm while mean baseline TDe value was 1.71 mm with a standard deviation of 0.22 mm. Study revealed a declining trend in diaphragmatic atrophy percentage over the course of ventilation (Table 1). On Day 2, the median daily diaphragmatic atrophy was 2.25%, with an interquartile range of 1.76% to 2.76%. As the days progressed, the atrophy percentage generally decreased. By Day 14, the median daily atrophy decreased to 0.73%, with an interquartile range of 1.76% to 2.76%. The overall trend suggested that diaphragmatic atrophy tends to decrease over time during the ventilation period. However, it's important to note that the number of subjects evaluated decreased as well, indicating a potential drop in sample size or patient availability as the study progressed. The median daily atrophy percentage for the entire period was 2.2%, with an interquartile range of 1.83% to 2.95%.

Our study also revealed a declining trend in diaphragmatic atrophy percentage over the course of ventilation (Figure 1). On Day 2, the median daily diaphragmatic atrophy was 2.25%, with an interquartile range of 1.76% to 2.76%. As the days progressed, the atrophy percentage generally decreased. By Day 14, the median daily atrophy decreased to 0.73%, with an interquartile range of 1.76% to 2.76%. The overall trend suggests that diaphragmatic atrophy tends to decrease over time during the ventilation period. The median daily atrophy percentage for the entire period was 2.2%, with an interquartile range of 1.83% to 2.95%.

In this study, mean TDi at baseline was 2.1 mm with a standard deviation (SD) of 0.2 mm, while the mean TDi pre extubation was 1.9 mm with an SD of 0.2 mm. The calculated difference in means was 0.19 mm (95% confidence interval 0.15-0.2), indicating a decrease in diaphragmatic thickness from baseline to pre extubation. A paired sample t-test was conducted to compare the means and the p-value for this comparison was found to be less than 0.01, indicating that the difference in means was statistically significant. Similarly, mean TDe at baseline was 1.71 mm with a standard deviation (SD) of 0.2 mm, while the mean TDe pre extubation was 1.58 mm with an SD of 0.2 mm. The calculated difference in means was 0.12 mm (95% confidence interval 0.09-0.16), indicating a decrease in diaphragmatic thickness from baseline to pre extubation. The p-value for this comparison came less than 0.01, signifying that the difference in means was statistically significant.

In this study, the baseline thickening fraction was 22.47%. Starting from Day 2, there was a progressive decrease in the thickening fraction percentage, reflecting a reduction in diaphragmatic thickening during ventilation. By Day 5, the thickening fraction decreased by 13.08%. Subsequently, there were variations in the thickening fraction, with some days showing slight increases or relatively stable values. On Day 10, there was a noticeable increase in the thickening fraction, which continued to rise on Day 11 and reached 7.17% by Day 12. On Day 14, there was a slight increase, reaching a percentage change of 3.03% (Figure 2).

Out of the forty six enrolled subjects thirty-eight had an evaluation of diaphragmatic parameters taken within twenty-four hours of extubation. The post extubation median value of TDi, TDe and Diaphragmatic thickening fraction were found significantly higher than pre extubation values. This suggested that there was a statistically significant trend towards early reversal of VIDD after extubation. The pre-extubation and post extubation values of TDi, TDe and DTF have been represented in figure 3, figure 4 and table 2.

We compared diaphragmatic atrophy in child ventilated for respiratory causes (n=18) versus for non-respiratory causes (n = 28), to see if lung pathologies itself could lead to increased atrophy.The p-values of thickening fraction values indicated no statistically significant differences between the two groups. The p-values range from 0.589 to 1.0, showing that there was no significant difference in TF between children ventilated for respiratory and non-respiratory.

In this study, out of forty six participants 13 experienced death while 33 survived. We tried to find relation between average daily atrophy rate at patient survival. In this study, Median Average daily atrophy % for the "Died" group was 2.4 and the Interquartile Range (IQR) for the "Died" group was 2.1-3.4. Median Average daily atrophy % for the

"Survived" group was 2.1 and the IQR for the "Survived" group was 1.8-2.6. A p-value of 0.067 suggested that there was some evidence of a difference between the two groups but the difference was not not statistically significant (Figure5).

Table 1 : Trend of diaphragmatic atrophy across days of ventilation

Day of Ventilation	Median Daily Diaphragmatic Atrophy %	Inter Quartile Range	Number of Subjects Evaluated
Day 2	2.25	1.76-2.76	46
Day 3	1.98	1.67-2.82	42
Day 4	2.30	1.64-2.76	33
Day 5	2.10	0.97-2.70	11
Day 6	1.57	1.08-1.45	8
Day 7	1.33	1.05-2.24	7
Day 8	1.38	1.13-2.29	5
Day 9	1.85	1.19-1.41	4
Day 10	1.38	1.05-2.02	4
Day 11	1.67	0.48-1.10	4
Day 12	0.73	0.49-1.01	4
Day 13	0.73	0.73-0.00	4
Day 14	0.73	1.76-2.76	3
Median Daily Atrophy	2.2	1.83-2.95	

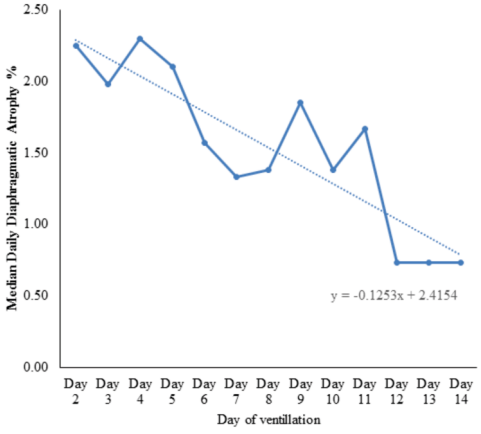

Figure 1: Median Daily Diaphragmatic Atrophy % Over Days of Ventilation (n=46)

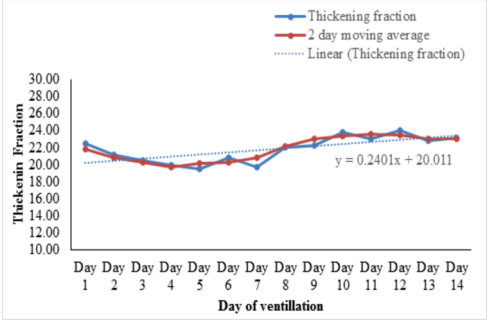

Figure 2: Assessment of Thickening Fraction Across Days of Ventilation (n=46)

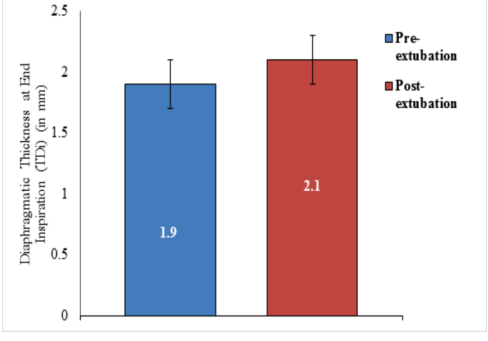

Figure 3: Distribution of Study Patients Based on Difference Between Pre-extubation and Post Extubation TDi
*Vertical bars indicate standard deviation

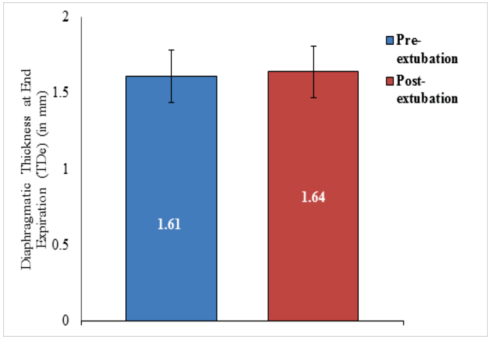

Figure 4: Distribution of Study Patients Based on Difference Between Pre-extubation and Post Extubation Tde
*Vertical bars indicate standard deviation

Table 2 : Difference between day 1 DTF and post extubation DTF

Diaphragmatic Thickening fraction (DTF)	Day 1 DTF		Post Extubation DTF		Difference in mean (95% CI)	p value*
	Mean	SD	Mean	SD		
	22.5	3.5	28.3	2.2	5.8 (4.7-6.9)	<0.01

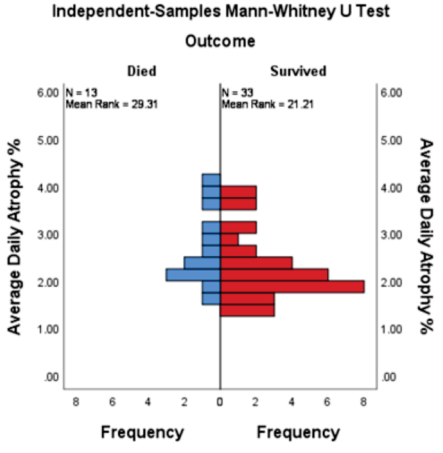

Figure 5: Distribution of Study Patients Based on Average Daily Atrophy and Outcome (n=46)

DISCUSSION

This prospective observational study was carried out in a tertiary PICU in northern India. With a sample size of forty six subjects, it was done primarily to assess the effect of mechanical ventilation on the diaphragm of pediatric patients. This study tried to evaluate if ventilator induced diaphragmatic dysfunction was occurring at similar rates as described in adult literature and a few small pediatric studies. Evaluation of VIDD was done primarily by assessing the diaphragmatic atrophy rate and thickening fraction.

The baseline values of diaphragmatic thickness found in our study (TDe 1.71mm) were higher than the values found by Mistri et al[14], similar to the values obtained by Lee et al[12] and lower than the baseline values found by Montoro et al[15] and Glau et al[3]. It is important to note that while conducting the same measurement the four studies have used slightly different techniques. The studies by Lee et al and Montoro et al, similar to our study, used the mid-point of the pleural and peritoneal layers to calculate baseline TDe and TDi. However, the study by Mistri et al used only the hypoechoic layer and excluded the pleura and peritoneal midpoint which may explain why the baseline TDe values were lower in this cohort. The higher values seen in the study by Glau et al are likely due to the fact that they have included the entire pleural and peritoneal layer in their measurement of values. However, the nutritional component as a cause of increased baseline values in western studies cannot be negated.

Our study was able to demonstrate significant diaphragmatic atrophy occurring in mechanically ventilated children. We found a daily atrophy rate of 2.25%. The findings of total atrophy are lower in our cohort than other pediatric studies (9.9% Mistri et al[14], 13.8% Glau et al[3] and 14% Montoro et al[15]) however we also had a lesser duration of MV (Median 4 days vs 6-8 days in other studies). When adjusted against the days of ventilation to calculate daily atrophy rates our

results were remarkably similar to values obtained by Montoro et al[15] (2%) and Mistri et al[14] (2.01%) and only slightly lower than the values of Glau et al[3] (3.4%). Adult literature meanwhile has reported higher rates of atrophy up to 6% per day[16], while other adult studies, such as Zambon et al[17] the values have ranged from -7.5% on CMV to +2.5% on PS. As shown by Zambon et al the differences in atrophy rates may be due to the general practice amongst pediatric intensivist to allow for high spontaneous breathing fraction and the frequent use partial support modes such as SIMV + PS rather than controlled ventilation. In a multivariable analysis, use of low levels of pressure support was associated with decreased diaphragm atrophy, supporting a role for spontaneous ventilation modes[3].

This study demonstrated a trend towards declining daily atrophy as the duration on MV proceeded. A similar trend was found in adult studies such as Schepens et al[18] who found a rapid fall in muscle mass in the initial 72 hours followed by a more gradual decline. This is also similar to what was seen in pediatric studies. Evaluation done by Mistri et al and Montoro et al also similarly found a gradually declining trend of daily atrophy. The rate of atrophy may also be declining due to the increased fraction of spontaneous breaths in the maintenance and weaning phases of ventilation. The initial rapid fall of muscle mass has also been attributed to the presence of "fewer type 1 fibers (slow-twitch, high-oxidative), which have higher oxidative capacity. The loss of sparse type 1 fibers immediately after intubation may result in poor resistance to diaphragmatic fatigue in children and the initial substantial deterioration of diaphragmatic contractions"[19].

Diaphragmatic thickening fraction is a direct index of contractility akin to the ejection fraction of the heart. We found a thickening fraction 22.47% which was slightly lower than the DTF range of 25 - 40% reported in adults at tidal breathing[20].

This study also examine the effect of extubation on the diaphragmatic indices, as we took a reading 12 to 24 hours after extubation. We found a significant improvement in both the muscle mass (1.61mm to 1.64mm) and DTF (22.5% to 28.3%) within 24 hours of liberation from ventilation. It was consistent with adult studies which have shown a rapid recovery in muscle mass and contractility after extubation[21]. Similarly, Montoro et al[15] who evaluated the diaphragm one week after extubation found that the TDe increased from 1.4 to 1.65mm and the DTF improved from 30% to 43%. Lee et al[12], further analyzed the recovery in DTF post extubation as a predictor for successful extubation. They found that "DTF < 17% immediately after extubation could predict the need for reintubation. Although low validity was obtained for the DTF cut off value for predicting extubation failure (only three cases of extubation failures were noted), this cut off can provide useful clinical information for predicting the need for reintubation". This may be used as a indicator for further interventions, such as need for NIV to avoid reintubations.

It is important to acknowledge the limitations of this study. Firstly, due to the small sample size the study was not powered to further analyze the various predictors of diaphragmatic atrophy, even though the sample size was comparable to other similar studies. Secondly, we did not analyze various other parameters that may have affected the diaphragmatic function such as steroid or inotropic use and severity scores that may have had a bearing on the final outcome. Finally, since the difference in measurement were only a few millimeters, despite using a standardized USG protocol we cannot guarantee the reproducibility of our data values.

CONCLUSION

Ultrasonography is an excellent non invasive tool to evaluate diaphragmatic function. Larger, well powered future studies are required to identify various predictors of atrophy and ventilatory strategies that can be used to minimize the effects of VIDD. There is a need to follow up the children for a longer period post extubation to determine when the diaphragmatic indices return to baseline values.

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