

PREVENTION OF RESPIRATORY MUSCLE DYSFUNCTION DUE TO DIAPHRAGM ATROPHY IN CHILDREN WITH RESPIRATORY FAILURE

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Abstract

The aim of the study was to determine whether diaphragm-protective mechanical ventilation can prevent diaphragm atrophy in children with respiratory failure.

Materials and methods. We complete the prospective single-center cohort study. Data analysis included 82 patients 1 month – 18 years old, divided into I group (lung-protective MV) and II group (diaphragm-protective in addition to lung-protective MV).

Patients were divided into age subgroups. Stages of the study: 1st day (d_1), 3rd (d_3), 5th (d_5), 7th (d_7), 9th (d_9), 28th (d_{28}). We studied changes in diaphragm thickness at the end of exhalation and compared them with these indicators at patient's admission to the study (baseline). Primary endpoint was length of stay in ICU, secondary endpoints were complications (prolonged MV). Results are described as arithmetic mean (\bar{X}) and standard deviation (σ) with level of significance p .

Results. There were significant differences in length of stay in ICU among patients of the 1st and 5th age subgroups: in 1st age subgroup this data was in 1.3 times lower in II group, compared with I group ($p < 0,05$); in 5th age subgroup the situation was the opposite – length of stay in ICU was in 1.4 times higher in II group, compared with I group ($p < 0.05$). There were no patients who required lifelong mechanical ventilation in any of the groups.

Changes in the thickness of the diaphragm, which indicate its atrophy, were the most significant among patients of the first, second, third and fourth age subgroups and the severity of atrophy was higher among patients of group I, compared with patients of group II.

Conclusions. Diaphragm-protective mechanical ventilation significantly prevents diaphragm atrophy in children with respiratory failure in 2nd, 4th, and 5th age subgroups. Providing goal-directed diaphragm-protective MV might reduce the length of stay in ICU among patients of 1st and 5th age subgroups. There were no observed complications like lifelong mechanical ventilation in both patient's group.

Keywords: respiratory muscles, respiratory failure, diaphragm atrophy, mechanical ventilation, weaning from mechanical ventilation.

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1. Introduction

Atrophy and weakness of the peripheral and respiratory muscles is well known problem in intensive care unit (ICU) [1]. Severe weakness of the diaphragm frequently occurs due to prolonged mechanical ventilation (MV) and lead to outcomes worsening and increased mortality rate [2, 3]. We know that diaphragmatic function is a major determinant of the ability to be successfully weaned from MV for patients [4]. However, despite thorough knowledge in molecular mechanisms of diaphragm injury due to MV, it is hard to find out the best clinical strategy how to prevent this complication. On the other hand, enough level of spontaneous breathing pattern function together with work of respiratory muscles might be a key how to solve this clinical problem. It seems to be possible to provide careful selection of MV parameters with taking into account diaphragm function for each patient.

The aim of the study was to determine whether diaphragm-protective mechanical ventilation can prevent diaphragm atrophy in children with respiratory failure.

2. Materials and methods

In January 2018 – April 2020 it was completed the prospective single-center cohort study at the Department of Anesthesiology and Intensive Care, Danylo Halytsky Lviv National Medical University; Department of Anesthesiology and Intensive Care, Lviv Regional Children Hospital «OCHMATDYT». We included patients with acute respiratory failure who was mechanically

ventilated. Exclusion criteria for the study were: the refusal of the patient's legal representatives to participate in the study at any of its stages, the patient's agonizing state upon admission, and a second trial of MV with its onset less than 48 h after prior weaning.

The study was conducted in accordance with the requirements of good clinical practice, the Council of Europe Convention on Human Rights and Biomedicine, the Helsinki Declaration of the World Medical Association. The study was approved by the Bioethics Commission of Danylo Halatsky Lviv National Medical University, protocol No. 1, January 30, 2018. All patients' relatives or their legal representatives signed informed consent to participate in the study.

The study included 89 patients aged 1 month – 18 years. All patients were randomly divided into 2 groups (using random.org). Group I included patients who received lung-protective ventilation strategy, group II – patients who received diaphragm-protective in addition to lung-protective ventilation strategy. 82 patients were included in the data analysis. We studied indicators of diaphragm function (amplitude of diaphragm movement and it was considered that decreasing of this indicator less than 8 mm was a marker of under-assistance during MV and increasing of this indicator over 15 mm was a marker of over-assistance during MV; thickening fraction and it was considered that decreasing of this indicator less than 15 % was a marker of diaphragm weakness; increasing it up to more than 35 % was a marker of high respiratory function and a potentially damaging factor for diaphragm), parameters of acid-base balance and mechanical ventilation.

We studied the relative changes in right hemidiaphragm thickness and compared them with the baseline data.

We divided patients into age subgroups: 1 subgroup – children 1 month – 1 year; 2nd subgroup – children 1–3 years; 3 subgroup – children 3–6 years; 4 subgroup – children 6–13 years; 5 subgroup – children 13–18 years.

Stages of the study: 1st day (d_1), 3rd day (d_3), 5th day (d_5), 7th day (d_7), 9th day (d_9), 28th day (d_{28}).

Primary endpoint was length of stay in ICU, secondary endpoints were complications (prolonged MV).

Statistical analysis of the study results was performed using MS Excel 2017 with the calculation of arithmetic mean (\bar{X}) and standard deviation (σ). Parametric criteria (Student's t-test) were used and the difference was considered statistically significant at $p < 0.05$.

3. Results

There were significant differences in length of stay in ICU among patients of the 1st and 5th age subgroups (**Table 1**): in 1st age subgroup this data was in 1.3 times lower in II group, compared with I group ($p < 0.05$); in 5th age subgroup the situation was opposite – length of stay in ICU was in 1.4 times higher in II group, compared with I group ($p < 0.05$).

Table 1

Primary endpoint, $\bar{X} \pm \sigma$

Criteria	Patient's age subgroup	I group	II group	P
Length of stay in ICU, days	1 st	16.3 ± 1.2	12.1 ± 0.3	0.03
	2 nd	9.8 ± 0.7	9.1 ± 0.3	0.22
	3 rd	13.2 ± 1.1	14.5 ± 1.2	0.51
	4 th	14.6 ± 1.3	11.4 ± 1.1	0.08
	5 th	8.5 ± 0.6	12.3 ± 1.6	0.04

There were no patients who required lifelong mechanical ventilation in any of the groups.

We analyzed the dynamics of changes of right hemidiaphragm thickness during the study (**Table 2**) and found that in 1st age subgroup in I group there was a tendency to decrease this indicator at stage d_3 from 3.3 ± 0.3 mm to 2.7 ± 0.2 mm, which mean 22.2 % decrease from baseline, and up to 2.0 ± 0.1 mm on d_9 , which was 65 % decrease from baseline. Whereas in II group, the

maximum decrease of diaphragm thickness was at the stage d_3 from 3.1 ± 0.2 mm to 2.9 ± 0.3 mm what was 6.9 % decrease from baseline. All differences between the I and II groups in 1st age subgroup were nonsignificant.

Table 2

Changes of right hemidiaphragm thickness along the study, $\bar{X} \pm \sigma$

Data	Patient's age subgroup	Study stage	Patient's group		P
			I	II	
Right hemidiaphragm thickness at the end of exhalation, mm	1 st	d_1	3.3 ± 0.3	3.1 ± 0.2	0.69
		d_3	2.7 ± 0.2	2.9 ± 0.3	0.16
		d_5	2.5 ± 0.1	3.1 ± 0.2	0.12
		d_7	2.4 ± 0.1	3.0 ± 0.1	0.08
		d_9	2.0 ± 0.1	3.2 ± 0.2	0.16
	2 nd	d_1	3.5 ± 0.3	3.2 ± 0.2	0.12
		d_3	2.8 ± 0.1	3.5 ± 0.2	0.04
		d_5	2.7 ± 0.2	3.3 ± 0.1	0.02
		d_7	2.9 ± 0.1	3.1 ± 0.2	0.25
		d_9	3.1 ± 0.1	3.3 ± 0.2	0.18
	3 rd	d_1	4.1 ± 0.1	4.0 ± 0.2	0.89
		d_3	3.2 ± 0.2	3.8 ± 0.2	0.21
		d_5	3.4 ± 0.1	3.9 ± 0.2	0.09
		d_7	3.3 ± 0.2	3.7 ± 0.1	0.1
		d_9	3.1 ± 0.2	3.9 ± 0.1	0.06
	4 th	d_1	4.9 ± 0.3	4.7 ± 0.2	0.39
		d_3	3.7 ± 0.1	4.8 ± 0.1	0.08
		d_5	3.8 ± 0.2	4.5 ± 0.3	0.02
		d_7	3.6 ± 0.1	4.6 ± 0.1	0.05
		d_9	3.9 ± 0.2	4.8 ± 0.1	0.001
	5 th	d_1	4.4 ± 0.3	4.6 ± 0.2	0.45
		d_3	4.1 ± 0.2	4.7 ± 0.3	0.02
		d_5	4.0 ± 0.1	4.2 ± 0.1	0.43
		d_7	4.2 ± 0.1	4.5 ± 0.3	0.18
		d_9	4.1 ± 0.2	5.1 ± 0.2	0.03

Changes in diaphragm thickness in 2nd age subgroup had the highest values in group I on stage d_5 when the thickness was 2.7 ± 0.2 mm compared with 3.5 ± 0.3 mm on stage d_1 , which was 29.6 % decrease from baseline values, and in group II the maximum decrease was achieved on stage d_3 and was 9.9 % from baseline. Diaphragm thickness values were significantly higher on study stages d_3 and d_5 in group II compared with group I.

In 3rd age subgroup the largest reduction in diaphragm thickness in I group was achieved on d_9 , when it was 32.3 % from baseline, whereas in II group the maximum reduction was 8.1 % on d_7 stage. All differences between I and II groups in 1st age subgroup were nonsignificant.

Among patients of 4th age subgroup the decrease in diaphragm thickness was the largest in I group on d_7 and was up to 36.1 % from baseline, while in II group – 11.9 % on stage d_5 . There were significant differences in diaphragm thickness in patients of I and II groups on stages d_5

and d_9 (**Table 2**): thickness was 3.8 ± 0.2 mm on d_5 in I group vs 4.5 ± 0.3 mm in II group ($p < 0.05$); and -3.9 ± 0.2 mm on d_9 in I group vs 4.8 ± 0.1 mm in II group ($p < 0.05$).

In 5th age subgroup the thickness of the diaphragm during the study decreased less significantly than in other age subgroups. The maximum decrease was registered in I and II groups on stage d_5 and were 10 % from baseline in I group and 9.5 % from baseline in II group and the differences between I and II groups were significant. The thickness of the right hemidiaphragm in I group was 4.1 ± 0.2 mm vs 4.7 ± 0.3 mm in II group ($p < 0.05$).

4. Discussion

Data on the prevalence of diaphragmatic atrophy in children with respiratory failure remain poorly understood, despite a significant number of publications on this clinical problem in adults [4, 5]. It is known, that weaning from MV depends on achievement a lot of parameters and the duration of MV is included in this list [6, 7]. As long we provide MV, as higher is the incidence weakness of diaphragm and its atrophy [8, 9]. Therefore, it is normal function of diaphragm during MV might improve outcomes in such patients.

Both the absence of diaphragm activity and excessive inspiratory effort can result in diaphragm muscle weakness, and recent evidence demonstrates that a moderate level of diaphragm activity during mechanical ventilation improves ICU outcome [10] and we in our previous study established that the prevalence and variety of manifestations of diaphragm dysfunction depend on the strategy of MV and low incidence of it was associated with lower duration of MV [11]. However, the other studies [12] found, that increasing age of child and presence of traumatic brain injury were associated with greater skeletal muscle loss in children on invasive MV. On the other hand, a great number of patients already are admitted to ICU with muscle weakness [13], and there are no data about this in paediatric population. Secondly, it is clear in adults that respiratory weakness is independently associated with long-term mortality [14], but we have no paediatric data about this. And low maximal inspiratory pressure is frequent in patients on MV mechanical ventilation due to muscles atrophy and is an independent risk factor for long-term mortality in ICU patients requiring mechanical ventilation [1, 14].

In addition to maintaining enough oxygenation level and elimination of CO_2 we have to prevent injury to the lung which is mediated by excessive mechanical stress and strain, on the other hand the diaphragm atrophy might develops as a consequence of low respiratory effort and injury in case of excessive effort [15]. The lung and diaphragm-protective mechanical ventilation approach aims to protect both organs simultaneously whenever possible.

One more option is diaphragm pacing in ICU patients. However, there is yet no clinical evidence of benefit from this method [16]. Direct stimulation of the phrenic nerves by surgically implanted electrodes has been employed to restore spontaneous ventilation in patients with high-level spinal cord injury and central hypoventilation syndrome. Recently, Reynolds et al. presented a first-in-human series of temporary transvenous phrenic nerve pacing in surgical patients and showed that this technology delivered safe and effective diaphragm contractions [17]. This strategy is currently being studied as potential intervention for improving diaphragm strength in difficult-to-wean patients.

One more approach to lung and respiratory muscle-protective ventilation is partial neuromuscular blockade [18, 19]. It is well known that complete neuromuscular blockade may increase the risk for diaphragm disuse atrophy and increases sedation requirements, whereas low-dose neuromuscular blockers («partial neuromuscular blockade») is an interesting compromise between total paralysis and strenuous breathing efforts [15].

In our study we found age-specific features of presence and severity of diaphragm atrophy during MV in children: in 1st, 2nd, 3rd and 4th age subgroup there were the most severe diaphragm atrophy in comparison with 5th age subgroup.

Limitations of the study. There were several limitations in the study. First, neither results assessor nor medical staff, who take care for patients, could not be blinded to group allocation because of the nature of the study. Second, the number of patients, who were included in the study, have to be enlarged in order to achieve significant differences in data which we studied.

Prospects for further research. Further studies are required to evaluate whether diaphragm atrophy might have impact on 28-days mortality rate in different age subgroups of children.

5. Conclusions

1) Diaphragm-protective mechanical ventilation significantly prevents diaphragm atrophy in children with respiratory failure in 2nd, 4th, and 5th age subgroups. In 2nd age subgroup on d_3 it was reached 29.6 % (I group) vs 9.9 % (II group) decreasing diaphragm thickness from baseline ($p < 0.05$); in 4th age subgroup on d_5 – 28.9 % from baseline (I group) vs 4.4 % (II group), $p < 0.05$; in 5th age subgroup on d_9 – 7.3 % decreasing from baseline (I group) vs 10.9 % increasing from baseline (I group), $p < 0.05$.

2) Providing goal-directed diaphragm-protective MV might reduce the length of stay in ICU among patients of 1st and 5th age subgroups.

3) There were no observed complications like lifelong mechanical ventilation in both patient's group.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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