DIAPHRAGMATIC MYOTRAUMA IN CHILDREN WITH ACUTE RESPIRATORY FAILURE

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Abstract

The aim of the study was to establish the prevalence of diaphragmatic dysfunction (DD), depending on the strategy of mechanical ventilation (MV).

Materials and methods. We completed 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 (d1), 3rd (d3), 5th (d5), 7th (d7), 9th (d9), 14th (d14), 28th (d28). We studied amplitude of diaphragm movement; thickening fraction, parameters of acid-base balance and MV. Results are described as median [IQR - interquartile range] with level of significance p.

Results. In patients of the 1st age subgroup in I group there were episodes with under-assist during MV, while in II group diaphragm overload was registered only on d5.

In patients of 2nd subgroup in I group we found over-assist of MV with excessive work of the right hemidiaphragm and low contractions of left dome at all stages of study, while in II group – the only episode of diaphragmatic weakness on d3 due to under-assist of MV. In the 3rd subgroup the proper diaphragmatic activity in I group was restored significantly later than in II group. In 4th subgroup of I group there was episode of high work of diaphragm on d5, whereas in II group – all data were within the recommended parameters for diaphragm-protective strategy of MV. In 5th subgroup of I group excessive work of both right and left domes of diaphragm was significantly more often registered than in II group, however, in II group there were found episodes of both type changes – diaphragmatic weakness and excessive work.

Conclusion. The prevalence and variety of manifestations of DD depend on the strategy of MV. Low incidence of DD was associated with lower duration of MV: in 1st age subgroup in 1.5 times; in 2nd age subgroup – in 2.4 times; in 4th age subgroup – in 1.75 times; in 5th age subgroup – in 4.25 times.

Keywords: diaphragm, mechanical ventilation, children.

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1. Introduction

Diaphragm weakness is highly prevalent in critically ill patients. It may exist prior to ICU admission and may precipitate the need for mechanical ventilation but it also frequently develops during the ICU stay [1, 2]. In addition, severe weakness of the diaphragm is frequent in mechanically ventilated patients, in whom it contributes to poor outcomes including increased mortality [3, 4]. And taking into account that from 30 % to 64 % of children in PICU need mechanical ventilation (MV), this clinical issue is highly important nowadays [5].

The described problem can be solved with reducing the incidence of diaphragmatic dysfunction and maintaining normal ranges both amplitude of diaphragm movement and its thickening fraction during MV. It will be possible with careful titration of mechanical ventilation parameters and taking into account data of diaphragm function for each patient individually.

The aim of the study was to establish the prevalence of diaphragmatic dysfunction, which might lead to diaphragm damage in children with acute respiratory failure, depending on the strategy of mechanical ventilation.

2. Materials and methods

From January 2018 to April 2020 we 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 for more than 3 days. 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 the onset of MV 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 Halytsky Lviv National Medical University, protocol №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.

To assess age-dependent data, patients were divided 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 (d1), 3rd day (d3), 5th day (d5), 7th day (d7), 9th day (d9), 14th day (d14), 28th day (d28).

Results described in this article is the part of the clinical study "Diaphragm ultrasound and trends in electrolyte disorders and transthyretin level as a method to predict ventilation outcome in children: the prospective observational cohort study"; ISRCTN84734652.

Statistical analysis of the study results was performed using MS Excel 2017 with the calculation median [IQR – interquartile range], the level of significance p with Kruskal-Wallis test.

3. Results

According to thickening fraction of diaphragm, we identified age-specific features in children during MV: in patients of the first age subgroup in I group there were found weakness of right hemidiaphragm with compensatory excessive level of work for its left dome on d1and d9, on the other hand, in group II diaphragm overload was registered only at stage d5.

The amplitude of right hemidiaphragm movements (**Fig. 1**) had no significant differences between I and II groups of 1st age subgroup at all stages of the study ($p>0.05$), however, we observed a tendency to its gradually increasing from 3.5 [3.1; 4.5] mm on d1 to 12.4 [10.2; 12.9] mm on d9 in I group, and from 4.5 [3; 5] mm to 8.9 [6.8; 9.5] mm at the same stage in II group of patients.

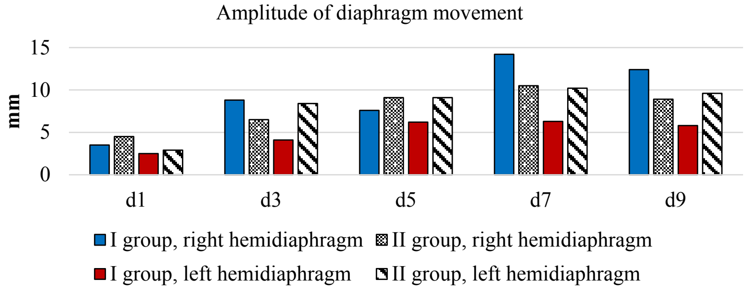

Fig. 1. The amplitude of right and left hemidiaphragm movement in 1st age subgroup of patients

At the same time, the amplitude of movements of left hemidiaphragm in 1st age subgroup increased and was significantly higher in II group on d3 with data 8.4 [7.3; 9.6] mm in comparison

with 4.1 [3.8; 4.5] mm in group I (p=0.04), and on d9 it was 9.6 [8.2; 12.2] mm in II group and 5.8 [4.1; 8.9] mm in I group (p=0.03).

In patients of 2nd age subgroup changes in I group were opposite to described previously – we found excessive work of the right hemidiaphragm with low contractions of left dome at all stages of study, while in II group – it was the only episode of diaphragmatic weakness on stage d3.

The amplitude of movements of the right hemidiaphragm (**Fig. 2**) in 2nd age subgroup had no significant differences between I and II groups at all stages of study. We found a tendency to gradually increase these indicators from stage d1 to stage d9. Data on the amplitude of movements of the left hemidiaphragm showed significant differences on d3 and d5 in patients of II group, and it was associated with inspiratory time decreasing on the same stages.

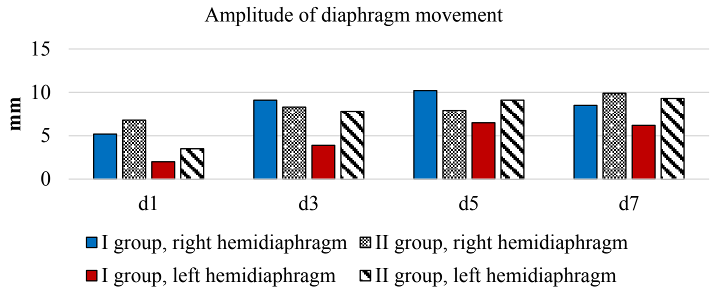

Fig. 2. The amplitude of right and left hemidiaphragm movement in 2nd age subgroup of patients

Thus, the amplitude of movements of left hemidiaphragm on d3 was 3.9 [2.5; 4.1] mm with inspiratory time 0.7±0.1 seconds in I group, in comparison with the amplitude 7.8 [3.8; 9.2] mm (p=0.01) and inspiratory time 0.45±0.01 seconds (p=0.02) in II group. Subsequently, inspiratory time in II group did not change until d9, and the amplitude of movements of left hemidiaphragm increased significantly in comparison with I group of patients on d5 (9.1 [8.5; 10] mm in II group, and 6.5 [5; 7.4] mm in I group, p=0.05.

In 3rd age subgroup, II group spontaneous diaphragm activity was restored significantly earlier from d1, and the fraction of thickening of right dome in this group was 19.4 [15.2; 21.4] % in comparison with the absence of contractions in I group (p=0.001). Similar situation was with left dome of diaphragm, when on d1 in I group it was in normal range, when in II group – 15.4 [6.5; 18] % (p=0.01). On d3, increasing of the thickening fraction of right and left domes of diaphragm were found significantly earlier among patients of II group, where the data were 24.5 [22,7; 31.5] % for right dome and 25.6 [22.5l 28.3] % for left dome, compared to 12 [9.4; 14.2] % for right and 18 [11.8; 21] % for left dome in I group (p=0.01 and p=0.03). From d5 to d9, the diaphragm thickening fraction in both groups was within the range recommended by the diaphragm-protective ventilation strategy. Summarizing all the above in 3rd age subgroup the proper diaphragmatic activity in I group of patients was restored later than in II group.

There were no significant differences between I and II groups of patients of 3rd age subgroup in amplitude of right dome of diaphragm movements (**Fig. 3**). Whereas for the left dome of the diaphragm, this data were significantly higher in II group on d7 and d9, it was associated with inspiratory time decreasing same stages.

In I group of 4th age subgroup there were found significantly higher fraction of thickening of both right and left domes of diaphragm on d5: for right dome it was 53.25 [26,5; 80] % compared to 31.3 [30.4; 35.7] % in II group; and 53.1 [41.7; 58.4] % in I group compared to 40.55 [22.2; 48.9] % in I group for the left dome of diaphragm (p=0.02 and p=0.02).

In addition, there were significantly higher amplitude of movements of both domes of diaphragm on d5 (**Fig. 4**): for the right dome it was 15.9 [14.6; 19.5] mm in group I, compared with 8.1 [7.5; 9.7] mm in group II (p=0.04); for the left dome of diaphragm – 22 [21,5; 23.5] mm in group I and 12 [9.5; 14] mm in group II (p=0.001).

In the 5th age subgroup in I group excessive work of both right and left domes of diaphragm was significantly more often registered during weaning than in II group, however, in II group were

found episodes of both type changes - diaphragmatic weakness and excessive work. The indicators of the diaphragm thickening fraction were high and exceeded the limits recommended for the diaphragm-protective strategy of ventilation in II group of patients on d1, d3 and d7: for right dome of the diaphragm it were 44.25 [35.7; 52.8] % compared to 25 [20.9; 30] % in group I (p=0.02) on d1; and 68.05 [66.7; 69.4] % compared to 18.05 [7.5; 60.7] % on d3 (p=0.001). On d7 in I group they were 54.6 [28.6; 80.6] % compared to 31.6 [23.5; 32.4] % in II group (p=0.001). The values of the thickening fraction of left diaphragm dome were also high on d1, d3 and d7.

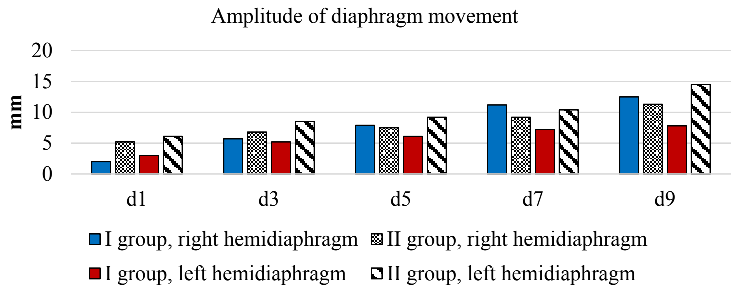

Fig. 3. The amplitude of right and left hemidiaphragm movement in 3rd age subgroup of patients

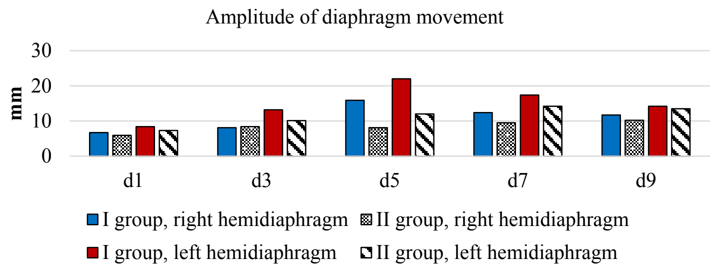

Fig. 4. The amplitude of right and left hemidiaphragm movement in 4th age subgroup of patients

The amplitude of diaphragm movements (**Fig. 5**) was below the recommended minimum value of 8 mm in both groups of patients till d5, and among patients of I group on d7 for the right and left domes, this data exceeded the recommended values 15 mm and was 18.1 [8.9; 21.9] mm for right dome and 18.5 [16.3; 19.4] mm for left dome, compared to 30.9 [12.5; 49.3] mm and 12.5 [11.2; 15.3] mm in II group. It was associated with a significantly higher inspiratory time in I group on these stages of the study.

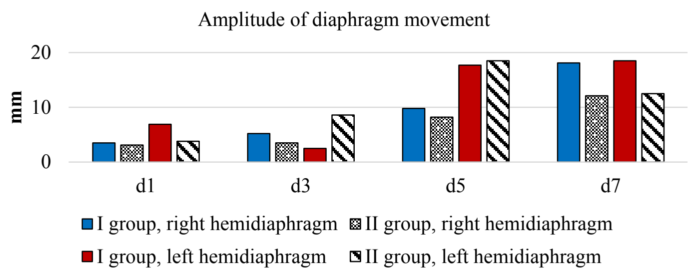

Fig. 5. The amplitude of right and left hemidiaphragm movement in 5th age subgroup of patients

Thus, use of diaphragm-protective strategy of MV in patients of the 5th age subgroup lead to reducing number of days when excessive work of the diaphragm was observed and therefore to avoid possible damage of diaphragm.

4. Discussion

This study identified possible mechanisms of diaphragmatic myotrauma in mechanically ventilated children. It is well known, that success of weaning from MV depends on age and dura-

tion of MV in children [6, 7]. On the other hand, as long we provide MV, as higher is the incidence of diaphragm atrophy and its weakness [8, 9]. Also, it was established that brief periods phrenic nerve stimulation (can improve mitochondrial function in the human diaphragm following MV [10]. Therefore, it is highly important to achieve normal function of diaphragm despite temporary life-saving respiratory support like MV. It might be implemented as diaphragm-protective strategy of MV [11, 12].

There are a lot of studies dedicated DD in adults discussing problem of acquired diaphragm dysfunction and its negative clinical impact on weaning outcome, length of mechanical ventilation (MV), survival and long-term outcome [13–16]. However, there are very little researches dedicated this issue among children. At the same time, criteria and tools for DD identification are the same for adult and children [17–19]. Moreover, pathophysiologically diaphragm-protective strategy in children is supported by recommendation to promote spontaneous breathing wherever its possible [20].

We found age-specific features of diaphragm dysfunction during MV in children: in 1st age subgroup I group there were episodes with under-assist during MV, which lead to weakness for right hemidiaphragm with compensatory excessive work for left its dome both at the beginning and at the end of MV. While in II group diaphragm overload was registered only on d5 and it might be due to over-assist during MV. It is interesting, that there are not precise cut off values that define safe ranges for inspiratory effort for adults [12]. Apart from this, safe thresholds of diaphragm activity to avoid under-assistance are absent. These limits are likely to vary per person depending on diaphragm strength. Nevertheless, common parameters that are used to define under-assistance are available and, as we proposed in our study, under-assist means thickening fraction of diaphragm have to be less than 10 %, while for over-assist – exceed 30 % [12].

In patients of 2nd age subgroup I group changes were the opposite to previous described – we found over-assist of MV with excessive work of the right hemidiaphragm with low contractions of left dome at all stages of study in I group, while in II group – the only episode of diaphragmatic weakness in stage d3 due to under-assist of MV.

In the 3rd age subgroup the proper diaphragmatic activity in I group of patients was restored later than in II group, therefore this patients need full assist with MV during this time. Goligher EC with colleagues (2015) and Schepens T et all., (2020) established, that unloading of diaphragm, more than the effects of MV itself, results in disuse atrophy and weakness. This is called overassistance myotrauma and affects about 50 % of patients receiving MV [12, 21, 22].

In the 4th age subgroup in I group there was episode of high work of a diaphragm at stage d5, which means over-assist with MV at this stage, whereas in II group – all data of diaphragm function were within the recommended parameters for diaphragm-protective strategy of MV at all stages of our study. So, in this age subgroup in II group it was achieved diaphragm-protective strategy during whole time of MV.

In the 5th age subgroup in I group excessive work of both right and left domes of diaphragm was significantly more often registered during weaning than in II group, however, in II group were found episodes of both type changes – diaphragmatic weakness and excessive work.

It was found that lower incidence of diaphragmatic dysfunction lead to decreasing duration of mechanical ventilation: in patients of the 1st age subgroup by 1.5 times (p=0.08); in patients of 2nd age subgroup – by 2.4 times (p=0.18); in 4th age subgroup – by 1.75 times (p=0.1); in 5th age subgroup – by 4.25 times (p=0.009). In patients of 3rd age subgroup duration of mechanical ventilation increased by 1.1 times (p=0.68). The frequency of complications (reintubations) was reduced in 1st age subgroup by 4.3 times (p=0.02); in 2nd age subgroup – by 3.4 times (p=0.04). There were no significant differences in the frequency of tracheostomy among patients of I and II groups.

Limitations of the study. Our current study has several limitations. 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-protective MV might improve clinical outcomes (length of stay in ICU, 28-days mortality

rate) in all age subgroups of children. In addition, it will be highly important to implement into clinical practice the rehabilitation of such patients.

5. Conclusion

1. The prevalence and variety of manifestations of DD depend on the strategy of MV. Diaphragm-protective strategy reduced the incidence of DD.

2. In case of diaphragm-protective MV the incidence of under-assist and over-assist in 1st, 2nd, 4th and 5th subgroups were low, while in 3rd subgroup – restoration of adequate spontaneous breathing occurs earlier.

3. Low incidence of DD in II group was associated with lower duration of MV: in 1st age subgroup in 1.5 times; in 2nd age subgroup – in 2.4 times; in 4th age subgroup – in 1.75 times; in 5th age subgroup – in 4.25 times. In patients of 3rd age subgroup duration of MV was increased in 1.1 times.

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CYTOKERATIN-18 AS A MARKER OF NON-ALCOHOLIC FATTY LIVER DISEASE IN OBESE ADOLESCENTS

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Abstract

In parallel with the obesity epidemic in the world, the prevalence of non-alcoholic fatty liver disease among children and adolescents is growing. Current data suggest that insulin resistance is one of the main factors in the pathogenesis of non-alcoholic fatty liver disease, and the content of fragments of caspase-cleaved cytokeratin-18 in the blood serum may be one of the informative indicators of non-alcoholic fatty liver disease progression.

The aim. To determine mechanisms of formation and progression of non-alcoholic fatty liver disease in obese children and adolescents by evaluating the level of cytokeratin-18.

Materials and methods. The study involved 46 adolescents with obesity and non-alcoholic fatty liver disease aged 12–17 years: 19 boys (41.3 %) and 27 girls (58.7 %). Clinical (weight, height, waist and hip circumference), laboratory (glucose, immunoreactive insulin, lipid metabolism, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, cytokeratin-18) parameters were studied and instrumental examination (abdominal ultrasound) was performed. To assess insulin resistance the triglyceride-glucose index was calculated.

Results. Depending on the presence of insulin resistance patients were divided into two groups: 21 (45.7 %) of adolescents with insulin resistance and 25 (54.3 %) of adolescents without insulin resistance. Blood tests in patients with insulin resistance revealed significantly higher levels of total cholesterol, triglycerides, very low-density lipoprotein cholesterol, fasting immunoreactive insulin, cytokeratin-18 and gamma-glutamyl transpeptidase. All adolescents were divided into 2 groups depending on the level of cytokeratin-18: patients with cytokeratin-18 >233 mIU/ml and <233 mIU/ml (15 (32.6 %) and 31 (67.4 %)