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Abstract.

Background: Acute respiratory failure due to pneumonia is a significant cause of death in children 6-18 years old. Objective: To find out whether diaphragm dysfunction might lead to unsuccessful weaning from MV in children 6-18 years old.

Materials and methods: We provided prospective observational cohort study and included 104 patients, who were splitting in the study and the control groups and 2 age subgroups. To consider diaphragm function, we check amplitude of its movement and diaphragm thickening fraction (Dtf).

The primary outcome was the incidence of successful weaning from MV. The secondary outcomes were changes in diaphragm function parameters.

Results: Dtf for right hemidiaphragm was significantly lower in the study group 1st subgroup on day 1 and day 5, and significantly higher on day 14 (p<0.05), while for left hemidiaphragm it was significantly higher on day 1 and lower on day 5 compared with the control group (p<0.05). In 2nd subgroup Dtf was significantly higher for both sides in the study group on day 1 compared with the control group (p<0.05).

Amplitude of diaphragm movement was significantly decreased in 1st subgroup of the study group on day 1 and day 5 and increased on day 14 compared with the control group (p<0.05).

The incidence of successful weaning from MV in the study group was significantly lower compared with the control group.

Conclusions: Diaphragm dysfunction might alter weaning from MV in children 6-18 years old.

Key words. Respiratory physiology, diaphragm, respiratory failure, children.

Introduction.

Diaphragm dysfunction is common in mechanically ventilated patients and predisposes them to prolonged ventilator dependence and poor clinical outcomes [1]. This fact was confirmed for adult patients and therefore diaphragm ultrasound becomes a daily routine investigation when patient is ready for decreasing mechanical ventilation (MV) parameters what means weaning from MV. Significantly, it has been observed that similar pathophysiology changes are present in pediatric patients, who need to be mechanically ventilated [2,3]. In the last decades we observed the improvement in the treatment of pediatric acute respiratory failure [2], and the mortality rates in children aged under 5 years have steadily declined in the WHO European Region in recent years, however, children are still dying from pneumonia [4]. There are guidelines on oxygen therapy for children [5], mechanical ventilation of critically ill children [6,7], nevertheless, there is no evidence that diaphragm dysfunction leads to complicated weaning from MV in children under 5 years old and how clinicians might improve clinical outcome in case of confirmed diaphragm dysfunction in child who is mechanically ventilated. The process of breathing is the work performed by the respiratory muscles, in particular the diaphragm. Exhaustion of such muscles leads to the impossibility of maintaining the proper level of breathing, and therefore, can lead to the persistence of respiratory insufficiency and complicate the process of weaning from mechanical ventilation. To confirm or deny the statement that diaphragm dysfunction impact weaning from mechanical ventilation we choose the study hypothesis that presence of diaphragm dysfunction might lead to unsuccessful weaning from respiratory support in children with acute respiratory failure.

Aim.

The aim of the study was to find out whether diaphragm dysfunction in patients with acute respiratory failure might lead to unsuccessful weaning from MV.

Materials and methods.

We provided prospective observational cohort study at the Department of Anesthesiology and Intensive Care, Danylo Haltsky Lviv National Medical University; Department of Anesthesiology and Intensive Care, Lviv Regional Children Hospital “OCHMATDYT” which included 104 patients 6 – 18 years old. There were 61 patients (study group) with acute respiratory failure who need to be provided with MV and 43 patients (control group) who underwent MV during elective surgeries and were weaned immediately after it were held. The main differences between the control and study groups were indications for mechanical ventilation. Patients without respiratory diseases and signs of acute respiratory failure were included in the control group, and they underwent mechanical ventilation during general anesthesia. The study group included those patients in whom the presence of acute respiratory failure was confirmed by clinical, laboratory, and instrumental examination methods, and mechanical ventilation was performed as a component of acute respiratory failure treatment. The control group of patients included children who underwent adenotonsillectomy, and the duration of ventilatory support did not exceed 80 minutes. In the study group there were included patients who were mechanically ventilated for more than 3 days due to severe bilateral community acquired pneumonia. The inclusion criteria for the study group were: $\text{paO}_2$ less than 60 mm Hg at high-flow nasal oxygen therapy, $\text{paO}_2/\text{FiO}_2$ ratio less than 250, shortness of breath more than 50% of the upper limit of the age-standard respiratory rate. Exclusion criteria for both groups 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. Both groups' patients received lung-protective ventilation strategy.

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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.

All patients were splitting in 2 age subgroups: 1st – 6 - 12 years old, 2nd – 13 - 18 years old. Patients were divided into age subgroups to take into account their age-related anatomical and physiological characteristics, in particular, the respiratory rate, lung compliance, chest elasticity. In our study, we do not present an analysis of changes in these indicators during the treatment course, however, the dynamics of these data were important in deciding on the duration of mechanical ventilation and initiation of weaning from it.

To check the diaphragm function, we provided ultrasonography of diaphragm during respiration and consider its amplitude of movement, diaphragm thickening fraction (Dtf), inspiratory time for both right and left hemidiaphragms. The primary outcome was the incidence of successful weaning from MV. The secondary outcomes were changes in diaphragm function parameters, which made the confirmation of the diaphragm dysfunction diagnosis. It was the amplitude of diaphragm movement (and decreasing less than 8 mm was a marker of under-assistance during MV, increasing over 15 mm was a marker of over-assistance during MV), and the diaphragm thickening fraction (decreasing less than 15% was a marker of diaphragm weakness and its increasing up to more than 35% was a marker of high respiratory function and a potentially damaging diaphragm factor).

Stages of the study: 1st day - for both groups and 5th day, 7th day, 14th day - for the study group only.

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. A p-value less than 0.05 was taken as statistically significant. Sample size calculations for our hypothesis resulted in 21 patients per group. We used a type 1 error of α = 0.05 and a power of 0.80 to calculate the sample sizes (G*Power version 3.3.9.4).

Results.

All participants completed the study protocol. For demographical data see Table 1. No adverse events were observed during the study. Diaphragm ultrasound data showed significant reduction of ventilator-patient asynchrony and, in addition, reduction the need in deep sedation after beginning weaning from MV in both groups but not significant difference between groups.

Diaphragm thickening fraction: Results are presented as median with IQR. Dtf for right hemidiaphragm was significantly lower in the study group 1st subgroup on day 1 and day 7 compared with the control group (p<0.05), and significantly higher on day 14 (p<0.05). On the other hand, for left hemidiaphragm Dtf in the study group was significantly higher on day 1 and significantly lower on day 5 compared with the control group (p<0.05) (Figure 1).

In 2nd subgroup Dtf was significantly higher for both right and left hemidiaphragms in the study group on day 1 compared with the control group (p<0.05) (Figure 2), while on day 5 and day 14 data were in normal reference ranges with no significant differences between groups.

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In 2nd subgroup Dtf was significantly higher for both right and left hemidiaphragms in the study group on day 1 compared with the control group (p<0.05) (Figure 2), while on day 5 and day 14 data were in normal reference ranges with no significant differences between groups.

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parameter had the tendency for increasing during the study for all subgroups of the study group. For 1st subgroup it increased from 4 [2; 6] mm on day 1 to 7 [6; 8] on day 5; 9 [7; 11] mm on day 7, and to 15 [11; 18] mm on day 14, while in 2nd subgroup from 9 [6; 11] mm on day 1 to 11 [6; 12] on day 5; 12 [8; 15] on day 7 and to 14 [8; 16] mm on day 14.

According to the obtained data, it could be stated that diaphragm dysfunction was detected in study group 1st subgroup on day 1 and day 5 with data about insufficient diaphragm load and on day 14 with data about diaphragm overload. Also, we found subclinical diaphragm overload in study group 2nd subgroup on day 14.

In the current study, there were found that the incidence of successful weaning from MV was 100% for the day 1 in the control group, while in study group the incidence was significantly lower (Table 3). In 1st subgroup successfully weaned from MV on day 14 were 20 out 22 patients (91%), in 2nd subgroup – 32 out 39 patients (82%). However, on day 1 – no one from the study group was weaned (0%), on day 5 – 4 out 22 patients in 1st subgroup (18%), 13 out 39 patients (33%) in 2nd subgroup; on day 7 – 12 out 22 patients in 1st subgroup (55%), 26 out 39 patients (67%) in 2nd subgroup (p<0.05).

Discussion.

In this prospective observational cohort study, we hypothesized that diaphragm dysfunction might lead to unsuccessful weaning from respiratory support in children with acute respiratory failure. The results showed that the presence of diaphragm dysfunction was significantly higher in patients with acute hypoxic respiratory failure compared with healthy individuals of the same age.

The diaphragm is the primary muscle of inspiration and therefore crucially determines the patient’s ability to sustain ventilation in the face of respiratory loads (acute or chronic). By prolonging ventilator dependence, dysfunction predisposes to further diaphragm atrophy and injury, to nosocomial complications (ICU-acquired weakness, nosocomial sepsis, so on), and to a higher risk of long-term morbidity and mortality [1]. It is well known that acute respiratory failure might lead to self-inflicted lungs injury [8] and diaphragm myotrauma [9] therefore the role of spontaneous breathing among patients with acute hypoxic respiratory failure is debated. On the other hand, there is no possibility to achieve readiness for weaning from MV without continuous training with increasing spontaneous breathing efforts and decreasing mechanical respiratory support. And the balance among these two processes is crucial in surviving patients and as soon as possible weaning from MV. Consequently, diaphragm ultrasound helps to check diaphragm function is highly important modern tool in ICU. Our study adds the important information that the presence of diaphragm dysfunction worsens clinical outcome due to decreasing the incidence of successful weaning from MV. These results might be expected beforehand, since data from previous studies in adult patients were published, where was established that diaphragm weakness can impact survival and increases comorbidities in ventilated patients [10]. Mechanical ventilation is linked to diaphragm dysfunction through several mechanisms of injury, referred to as myotrauma. By monitoring diaphragm activity and titrating ventilator settings, the critical care clinician can have a direct impact on diaphragm injury [1].

### Table 1. Personal data.

<table>
<thead>
<tr>
<th>Group (subgroup), n</th>
<th>Study (1st), n=22</th>
<th>Study (2nd), n=39</th>
<th>Control (1st), n=21</th>
<th>Control (2nd), n=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>14/8</td>
<td>24/15</td>
<td>7/8</td>
<td>8/8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>118 [112; 121]</td>
<td>151 [142; 156]</td>
<td>115 [111; 120]</td>
<td>155 [152; 159]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>22 [21; 25]</td>
<td>48 [42; 51]</td>
<td>27 [24; 29]</td>
<td>51 [45; 54]</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>15.5 [14.8; 17.1]</td>
<td>[20.9 [18.8; 22.1]</td>
<td>19.8 [18.5; 21.5]</td>
<td>21.1 [20.4; 23.1]</td>
</tr>
</tbody>
</table>

Table 2. Changes in diaphragm movement amplitude for the study and the control groups.

<table>
<thead>
<tr>
<th>Amplitude of diaphragm movement, arithmetic means for right and left sides, mm</th>
<th>1st</th>
<th>2nd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, day 1</td>
<td>9 [8; 10]</td>
<td>11 [8; 12]</td>
</tr>
<tr>
<td>Study, day 1</td>
<td>4 [2; 6]</td>
<td>9 [6; 11]</td>
</tr>
<tr>
<td>Study, day 5</td>
<td>7 [6; 8]</td>
<td>11 [6; 12]</td>
</tr>
<tr>
<td>Study, day 7</td>
<td>9 [7; 11]</td>
<td>12 [8; 15]</td>
</tr>
<tr>
<td>Study, day 14</td>
<td>15 [11; 18]</td>
<td>14 [8; 16]</td>
</tr>
</tbody>
</table>

Table 3. The successful weaning from MV incidence in the control and the study groups.

<table>
<thead>
<tr>
<th>Count of successfully weaned from MV patients/ total patients' count</th>
<th>1st</th>
<th>2nd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, day 1</td>
<td>15/15</td>
<td>16/16</td>
</tr>
<tr>
<td>Study, day 1</td>
<td>0/22</td>
<td>0/39</td>
</tr>
<tr>
<td>Study, day 5</td>
<td>4/22</td>
<td>12/39</td>
</tr>
<tr>
<td>Study, day 7</td>
<td>12/22</td>
<td>26/39</td>
</tr>
<tr>
<td>Study, day 14</td>
<td>20/22</td>
<td>32/39</td>
</tr>
</tbody>
</table>

Data presented as median with IQR or numbers when applicable.
Based on the results of this study, it seems that good diaphragm contraction quality with enough level of its movement amplitude facilitates smooth and quick liberation from respiratory support. So, the amplitude of diaphragm movement from 9 [8; 10] mm in 1st subgroup of the control group, 11 [8; 12] mm in 2nd subgroup of the same control group give 100% of successful weaning on day 1. Of course, these were patients with good lung compliance unlike the study group, where patients need to do high respiratory muscles’ work to maintain gas exchange in case of low lung compliance. The reason for lower incidence of weaning from MV till day 14 in 1st subgroup of the study group might be in pathophysiological features of respiratory system due to pneumonia. It is difficult to achieve a good level of ventilator-patient interaction due to psychological issues which lead to patient-ventilator asynchrony with excessive muscles work, what have the confirmation in high level of amplitude of diaphragm movement on 14 day in 1st subgroup study group with the high level of DfP on the same day 14, when the median for right side was 47% and for the left side - 38%. The theoretical confirmation of harmfulness the under assistance myotrauma are study about the effects of both chronic and acute load-induced diaphragm injury which have been demonstrated by muscle biopsies in healthy subjects and patients with chronic obstructive pulmonary disease (COPD) [11]. Contraction against an excessive load (isotonic/concentric loading) leads to acute diaphragm injury, inflammation, and weakness [11,12]. Critically ill patients are at especially high risk for load-induced injury as systemic inflammation renders the muscle fiber membrane (sarcolemma) more susceptible to injury [12]. In an experimental sepsis model, applying mechanical ventilation to relieve inspiratory loading significantly attenuates muscle fiber injury and diaphragm weakness [13]. In addition, patients with a thickening fraction value of 15–30% on average during the first 3 days of ventilation (like that of healthy subjects at rest) had stable diaphragm thickness and the shortest duration of ventilation [14].

Conclusion.

In conclusion, the optimal effort level to prevent diaphragm dysfunction is uncertain and may vary according to the patient's clinical condition. Several lines of evidence suggest that maintaining a relatively low effort similar to that of healthy study participants breathing at rest might be the most effective approach. Diaphragm dysfunction might have the impact on the weaning from MV, enabling enough level of respiratory muscles work to maintain spontaneous breathing. Using diaphragm protective MV strategy during weaning process might be helpful strategy to avoid diaphragm myotrauma and train it.

Assistance with the study.

The authors thank all of the pediatric anesthesiologists at the Department of Anesthesiology and Intensive Care, Lviv Regional Children Hospital “OCHMATDYT”, Lviv, Ukraine, for their cooperation in anesthesia and intensive therapy management.

Authors personal contribution.

Concept – Olha Filyk, Yaroslav Pidhirnyi
Data collection and analysis – Olha Filyk
Writing an article – Olha Filyk
Editing and approving the final version of the article – Olha Filyk, Yaroslav Pidhirnyi.

Permission of the Bioethics Commission to conduct research.

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.

Conflicts of interest. None.

Financial support and sponsorship. None

REFERENCES

5. Pneumonia accounts for 12% of all deaths in children under 5 in European Region.
ФУНКЦИЯ ДЫХАТЕЛЬНЫХ МЫШЦ У ДЕТЕЙ 6-18 ЛЕТ С ОСТРОЙ ГИПОКСЕМИЧЕСКОЙ ДИХАЛЬНОЙ НЕДОСТАТОЧНОСТЬЮ: ПРОСПЕКТИВНОЕ ОБСЕРВАЦИОННОЕ КОГОРТНОЕ ИССЛЕДОВАНИЕ

Резюме

Введение. Острая дыхательная недостаточность, вызванная пневмонией, является значимой причиной смерти детей в возрасте 6-18 лет.

Целью исследования было установить, приводит ли дисфункция диафрагмы к неудачному отлучению от ИВЛ.

Материалы и методы. Мы провели проспективное обсервационное когортное исследование, в которое было включено 104 пациента. Все пациенты были разделены на основную и контрольную группы, а также на две возрастные подгруппы. Функцию диафрагмы устанавливали по показателям амплитуды движений ее куполов и фракции истончения.

Первичным конечным результатом исследования была частота успешного отлучения от ИВЛ. Вторичными конечными результатами исследования были изменения показателей функционирования диафрагмы.

Результаты. Показатель фракции истончения для правого купола диафрагмы был достоверно ниже в 1-й подгруппе основной группы на 1-й и 5-й дни и достоверно выше на 14-й день (р<0,05), тогда как для левого купола диафрагмы - достоверно выше на 1-й день и достоверно ниже на 7-й день по сравнению с контрольной группой (р<0,05). Во 2-й подгруппе основной группы показатель фракции истончения для обоих куполов был достоверно выше на 1 день по сравнению с контрольной группой (р<0,05).

Показатель амплитуды движений диафрагмы был достоверно ниже в 1-й подгруппе основной группы на 1-й и 5-й день и достоверно выше на 14-й день по сравнению с контрольной группой (р<0,05). Установлено, что частота успешного отлучения от ИВЛ в основной группе была достоверно ниже по сравнению с контрольной группой.

Выводы. Наличие дисфункции диафрагмы может влиять на результаты отлучения от ИВЛ у детей 6-18 лет.

Ключевые слова: физиология дыхания, диафрагма, дыхательная недостаточность, дети.