ORIGINAL ARTICLE

DIAPHRAGM FUNCTION IN CHILDREN WITH ACUTE HYPOXEMIC RESPIRATORY FAILURE: THE PROSPECTIVE OBSERVATIONAL COHORT STUDY

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ABSTRACT

The aim: To find out whether diaphragm dysfunction might lead to unsuccessful weaning from MV.

Materials and methods: We provided prospective observational cohort study and included 105 patients and divided them in the study and the control groups. 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: 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. Successfully weaned from MV in the study group among children 1 month - 1 year old on day 14 were 20 out 28 patients (71%), in children 1 - 3 years old - 9 out 11 patients (82%), in children 3 - 5 years old - 15 out 15 (100%). However, on day 1 - no one from the study group was weaned (0%), on day 7 - 5 out 28 patients 1 month - 1 year old (18%), 6 out 11 patients (55%) 1 - 3 years old, and 8 out 15 patients (53%) 3 - 5 years old ($p<0.05$).

Conclusions: Diaphragm dysfunction might alter weaning from MV.

KEY WORDS: children, diaphragm, respiratory failure, respiratory physiology

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INTRODUCTION

Patients who are admitted to an ICU frequently exhibit muscle weakness, and the respiratory muscles are often affected. [1]. On the other hand, mechanical ventilation (MV) is associated with diaphragm injury and its mechanism might be complex and is due to myotrauma [2]. Both these clinical problems frequently occur in mechanically ventilated patients and predisposes them to prolonged ventilator dependence and poor clinical outcomes [3] and the presence of either insufficient or excessive diaphragmatic contractile effort plays a central role in this process [4]. These facts were confirmed for adults, therefore assessing diaphragmatic function with ultrasound is a routine investigation when patient is ready for decreasing MV parameters and weaning from MV. Significantly, it has been observed that similar pathophysiology changes are present in pediatric patients, who need to be mechanically ventilated due to acute or chronic respiratory failure [5, 6]. In the last decades we observed the improvement in the treatment of pediatric acute respiratory failure [5], and the mortality rates in children under 5 years old have steadily declined in the European Region. However, children are still dying from acute respiratory failure caused by pneumonia [7] despite the presence of modern guidelines on oxygen therapy for children [8] and mechanical ventilation of critically ill children [9]. Nevertheless, there is no a littke knowledge about diaphragm dysfunction in children, admitted to ICU and no evidence that diaphragm dysfunction leads to complicated weaning from MV.

The study hypothesis was that diaphragm dysfunction could not lead to unsuccessful weaning from respiratory support in children with acute respiratory failure.

THE 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 and included 105 patients 1 month – 5 years old. Study group (n=54) included patients with acute respiratory

failure due to pneumonia, who need to be provided with MV over 72 hours. Control group (n=51) included patients, who underwent short term MV (less than 2 hours) during elective otolaryngology or urology surgery, had no risk factors of diaphragm dysfunction (severe malnutrition, congenital neuro-muscular diseases, onset of ICU admission during last 6 months), and were weaned from MV after surgery were held. 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, protocol №1, January 30, 2018. All patients` relatives or their legal representatives signed informed consent to participate in the study.

For demographical data we divided all patients into age subgroups (Table I). It was established risk factors of diaphragm dysfunction, selected MV parameters according body weight and height, individualized treatment.

Both groups received lung-protective mechanical ventilation with pressure control ventilation mode (PCV), study group - with "Hamilton C1" or "Hamilton C3", control group – with "Leon" anesthetic machine. Parameters of MV in both groups depended on oxygenation and CO_2 elimination. In addition, in the study group we took into account lung compliance and airways resistance data. The parameters of MV across research in the study group depended on oxygenation, CO_2 elimination, acid-base analysis, course of the disease and ranged: PIP from 18 to 26 cm H_2O; PEEP from 7 to 14 cm H_2O; Rate from 32 to 20 per min; Tin from 0.5 to 1.4 sec; Pplat from 16 to 24 cm H_2O; TV= 5-7 ml/kg; FiO_2 from 0.65 to 0.4; while in the control group MV parameters were more predictable and ranged: PIP = 16-18 cm H_2O; PEEP = 3-4 cm H_2O; Rate = 22 – 28 per min; Tin = 0.5 – 1.1 sec; TV = 6-7 ml/kg; FiO_2 = 0.6.

For the structural and functional assessment of the diaphragm we used ultrasonography of diaphragm during respiration: in the study group – 10:00 – 11:00 AM after suctioning and then 30 minutes rest with the as minimal as possible sedation level and as best as possible spontaneous breathing efforts level but not less than 60% of spontaneous minute volume ventilation; in the control group – 9:00 – 12:00 AM after restoration of spontaneous breathing after surgery with light sedation and achieving over 60% of spontaneous minute volume ventilation. The ultrasound examinations were carried out by two experienced investigators using a commercially available Vivid S60N, GE Healthcare, Milwaukee, Wl, USA with curvilinear transducer 3-5 MHz, 60-mm curved array. Patients were in supine position and transducer was placed in L3 (lung zone 3, 4^{th}-10^{th} intercostal spaces, between the anterior and posterior axillary lines), marker pointing cephalad. We search for the interface between the diaphragm and lung at about 5th to 8th intercostal space with identification of lungs, diaphragm, liver, and spleen. Both side examination with B-mode for identification of structures and M-mode for diaphragm function evaluation were used. We measured amplitude of diaphragm movement and inspiratory time with calculation of diaphragm thickening fraction (Dtf), which reflects the magnitude of diaphragmatic effort, for both right and left hemidiaphragms.

Dtf was calculated as percentage from the formula: (thickness at end-inspiration – thickness at end-expiration)/thickness at end expiration × 100.

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 Dtf (decreasing below 15% was a marker of diaphragm weakness and its increasing over 35% - a marker of high respiratory function and a potentially damaging diaphragm factor).

Stages of the study: 1^{st} day, 7^{th} day, 14^{th} day. We compared study and control group only on the 1^{st} day. Next stages we used to compare changes over time only for the study group.

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. The D' Agostino test was used to assess the normality of continuous variables. Descriptive statistics are presented as mean ± SD, median [IQR] or numbers (%), as appropriate. Continuous variables were compared with Student's *t*-tests or Mann–Whitney *U*-tests. All statistical analyses were performed using SPSS (SPSS 23.0; IBM Inc., Armonk, New York, USA) software,and *P* value less than 0.05 was considered statistically significant.

RESULTS

All participants completed the study protocol. No adverse events were observed during the study. Dia-

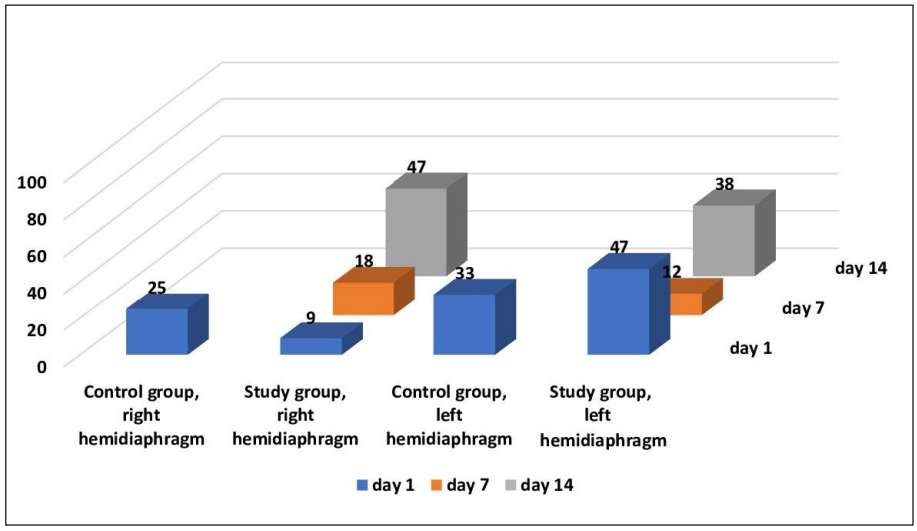

Fig. 1. Children 1 month - 1 year

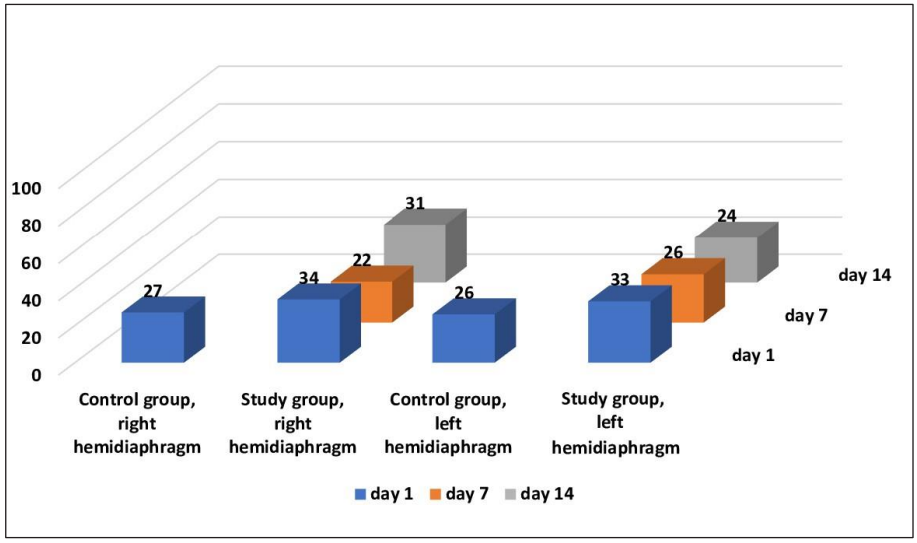

Fig. 2. Children 1-3 years old

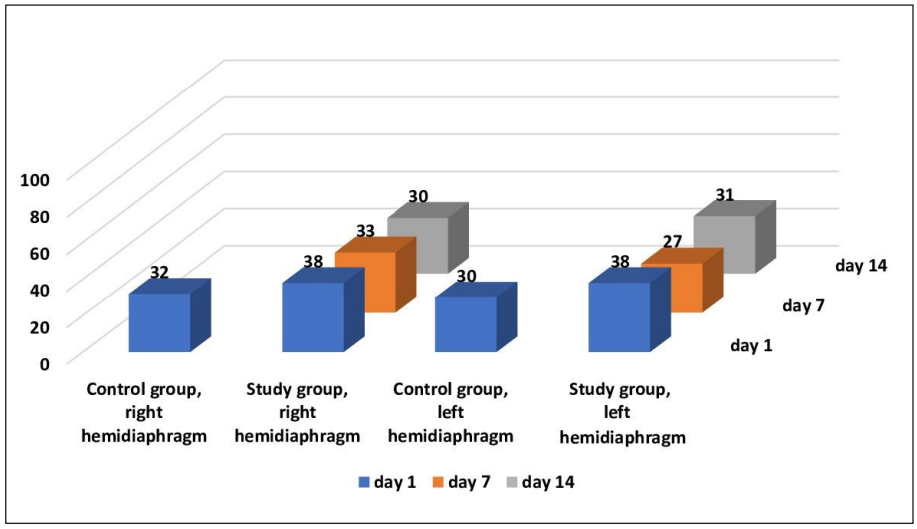

Fig. 3. Children 3-5 years old

phragm 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 in children 1 month – 1 year old on day 1 compared with the control group ($p<0.05$), and significantly

Table I. Personal data

	Group (age), n					
	Study (1 month – 1 year old), n=28	**Study (1 – 3 years old), n=11**	**Study (3 – 5 years old), n=15**	**Control (1 month – 1 year old), n=15**	**Control (1 – 3 years old), n=16**	**Control (3 – 5 years old), n=20**
Sex (male/female)	18/10	7/4	9/6	10/5	8/8	12/8
Age (months)	1.8 [1.2; 2.9]	14.5 [12.5; 19.0]	39.5 [37.0; 44.5]	2.1 [1.5; 2.8]	15.1 [13.5; 21.0]	41.5 [38.0; 46.5]
Height (cm)	55 [53; 56]	71 [68; 73]	95 [92; 99]	55 [52; 58]	72 [69; 74]	99 [93; 102]
Weight (kg)	4.1 [3.6; 4.3]	9.9 [8.9; 11.5]	14.2 [13.2; 16.5]	4.2 [3.4; 4.4]	11.1 [9.5; 11.8]	15.4 [14.6; 16.9]
BMI, kg/m^2	13.8 [13.4; 14.1]	19.8 [19.2; 20.2]	15.8 [14.9; 16.2]	13.9 [13.6; 14.2]	21.9 [18.7; 22.4]	16.1 [15.4; 18.9]

* Data presented as median with IQR or numbers when applicable.

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

Data	**Age**	**Group, study stage**				**P**
		Control, day 1	**Study, day 1**	**Study, day 7**	**Study, day 14**	**(for control and study groups on day 1)**
Amplitude of diaphragm movement, arithmetic means for right and left sides, mm	1 month – 1 year old	8 [6; 10]	3 [2; 5]	5 [3; 8]	18 [13; 20]	0,04
	1 – 3 years old	10 [9; 11]	6 [5; 9]	8 [6; 11]	11 [9; 15]	0,12
	3 – 5 years old	14 [8; 16]	7 [6; 9]	10 [7; 12]	16 [12; 19]	0,03

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

Data	**Subgroup**	**Group, study stage**				**P (for control and study groups on day 1)**
		Control, day 1	**Study, day 1**	**Study, day 7**	**Study, day 14**	
Count of successfully weaned from MV patients/ total patients` count	1 month – 1 year old	15/15	0/28	5/28	20/28	0,04
	1 – 3 years old	16/16	0/11	6/11	9/11	0,02
	3 – 5 years old	20/20	0/15	8/15	15/15	0,03

higher across the research on day 14 in comparison with day 7 in the study group ($p<0.05$). On the other hand, for left hemidiaphragm Dtf was significantly higher on day 1 in the study group compared with the control group ($p<0.05$) (Fig.1).

In children 1 year – 3 years old in the study group Dtf was significantly higher for both right and left hemidiaphragms on day 1 compared with the control group ($p<0.05$) (Fig.2). On day 7 and day 14 data were in normal reference ranges with no significant differences between this study stages for the study group.

Dtf for right and left hemidiaphragms in children 3 years- 5 years old in the study group has no significant differences with the control group on day 1 and no significant differences across the research in study group (Fig.3).

The analysis of the incidence the absence of spontaneous movements of diaphragm in study group showed, that 3 out 28 patients1 month – 1 year old, 1 out 11 patients 1 – 3 years old, and no one out 15 patients 3-5 years old have this deterioration on day 1. No such kind changes were observed on next study stages.

AMPLITUDE OF DIAPHRAGM MOVEMENT

Results are presented as median with IQR. We have made the analysis of data on right and left sides, they were very close for every patient, therefore we present arithmetic means for both sides diaphragm movement amplitude.

No statistically significant differences were found between groups in children 1-3 years old across the research (Table II).

We compared the amplitude of diaphragm movement across the research in children 1 month – 1 year old in the study group and found out that data were significantly decreased on day 1 and day 7 ($p<0.05$), and significantly increased on day 14 in comparison with day 7 ($p<0.05$) (Table II). In addition, this parameter had the tendency for increasing during the research for all patients in the study group. In particular, in children 1 month – 1 year old it increased from 3 [2; 5] mm on day 1 to 5 [3; 8] mm on day 7, and to 18 [13; 20] mm on day 14, while in children 1 – 3 years old - from 6 [5; 9] mm on day 1 to 8 [6; 11] on day 7 and to 11 [9; 15] mm on day 14. In children 3-5 years old these data were 7

[6; 9] mm on day 1, 10 [7; 12] mm on day 7, and 16 [12; 19] mm on day 14.

According to the obtained data, it could be stated that diaphragm dysfunction was detected in children 1 month – 1 year old in the study group on day 1 and day 7 with confirmation of insufficient diaphragm load and on day 14 with confirmation of diaphragm overload. Also, we found subclinical diaphragm overload in children 1 – 3 years old on day 1. There were no found data about diaphragm dysfunction in children 3-5 years old in the study group. There were no found data about diaphragm dysfunction in the control group.

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 III). Successfully weaned from MV in the study group among children 1 month – 1 year old on day 14 were 20 out 28 patients (71%), in children 1 – 3 years old – 9 out 11 patients (82%), in children 3 – 5 years old – 15 out 15 (100%). However, on day 1 – no one from the study group was weaned (0%), on day 7 – 5 out 28 patients 1 month – 1 year old (18%), 6 out 11 patients (55%) 1 – 3 years old, and 8 out 15 patients (53%) 3 – 5 years old ($p<0.05$).

DISCUSSION

In this prospective observational cohort study, we hypothesized that diaphragm dysfunction could not lead to unsuccessful weaning from respiratory support in children with acute respiratory failure. The results showed, to the contrary, that the presence of diaphragm dysfunction was significantly higher in patients with acute hypoxemic 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 [3]. It is well known that acute respiratory failure might lead to self-inflicted lungs injury [11] and diaphragm myotrauma [12] therefore the role of spontaneous breathing among patients with acute hypoxemic 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 successfull 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 [13]. 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 [3].

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 8 [6, 10] mm in infants in the control group, 10 [12, 13] mm in 1-3 years old children of the same control group, and 14 [11, 18] mm in children 3 – 5 years old in the control group on day 1 give 100% of successful weaning. 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 children 1 month – 1 year old in the study group might be in physiological features of respiratory system for this age. 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 infants in the study group with the high level of Dtf 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 underassistance 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 [13, 14]. 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 [14]. In an experimental

sepsis model, applying mechanical ventilation to relieve inspiratory loading significantly attenuates muscle fiber injury and diaphragm weakness [15]. In addition, patients with a thickening fraction value of 15–30% on average during the first 3 days of ventilation (similar to that of healthy subjects at rest) had stable diaphragm thickness and the shortest duration of ventilation [16].

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.

CONCLUSIONS

Diaphragm dysfunction seems to alter the weaning from MV, enabling enough level of respiratory muscles work to maintain spontaneous breathing. Using diaphragm protective MV strategy during weaning process will be helpful to avoid diaphragm myotrauma.

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Conflict of interest:

The Authors declare no conflict of interest.

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