Ultrasound Assessment of Diaphragm Function in Traumatic Brain Injury: A Prospective Observational Study

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Abstract

Background   Prolonged mechanical ventilation is associated with weaning failure in severe TBI patients. Ultrasound is a noninvasive modality for evaluating diaphragm function. On ultrasonography (USG), diaphragm thickness is observed to decrease over time in mechanically ventilated patients. However, little literature exists on the severity of diaphragmatic dysfunction in traumatic brain injury (TBI) patients. This study aimed to observe the changes occurring in diaphragmatic function in mechanically ventilated TBI patients.

Methods   TBI patients aged 18 to 65 years, requiring mechanical ventilation, were included. USG assessment of diaphragm function was done on days 0, 3, 5 and 7 of neurotrauma intensive care unit (NICU) admission in the supine position, during sedation holiday and spontaneous breathing trial. Measurements were done at end expiration (T_E) and at maximal inspiration (T_I) using 7- to 13-MHz linear array probe for three consecutive times and then averaged. Thickness fraction was calculated as $(T_I - T_E/T_E) \times 100$. Diaphragmatic excursion (DE) was measured in the M mode using 1- to 5-MHz phased array probe, as maximal height of inspiration.

Results   Forty patients were evaluated. The mean diaphragmatic thickness fraction (DTF) at days 0, 3, 5, and 7 was 33.58 ± 10.08, 33.4 ± 9.76, 32.32 ± 8.36, and 31.65 ± 8.23, respectively. Change in DTF was statistically significant on day 7 ($p = 0.040$). The mean DE at days 0, 3, 5, and 7 was 9.61 ± 3.99, 9.02 ± 3.46, 8.87 ± 2.63, 8.56 ± 2.74, respectively. Changes in DE over days 3, 5, and 7 were statistically significant ($p < 0.001$). The mean DTF was lower on day 3 in patients who were admitted for less than 20 days than those who required hospital admission for more than 20 days ($p = 0.044$).

Conclusion   Decrease in DTF and DE over the period of 7 days was observed with a significant decrease occurring on the 7th day following TBI.

Keywords

► diaphragmatic dysfunction
► diaphragmatic excursion
► diaphragmatic thickness fraction
► mechanical ventilation
► ultrasound

Introduction

Patients suffering from severe traumatic brain injury (TBI) often require prolonged mechanical ventilation due to low Glasgow coma score (GCS) to prevent secondary brain insults and for prophylactic hyperventilation.[1] Although lifesaving, the prolonged mechanical ventilation is often associated with weaning failure in up to 38% of severe TBI patients.[2] This failure can be attributed to either central nervous system (CNS) pathology or ventilator-induced diaphragmatic dysfunction (VIDD) resulting from disuse atrophy.[3] In a pilot study, it was found that as many as 64% of patients with TBI had diaphragm atrophy.[4] The pathophysiology of VIDD is poorly understood. Studies have shown that increased proteolysis of muscle fibers, decrease blood supply to the diaphragm, or oxidative stress may be responsible for VIDD.[5]

Various methods available to assess the diaphragmatic function include phrenic nerve stimulation, transdiaphragmatic pressure measurement, fluoroscopy, and electrophysiological measurement. These methods are underutilized due to their invasive nature, radiation exposure, and requirement to transport patients outside neurotrauma intensive care unit (NICU). Ultrasound (US) has emerged as a noninvasive modality to evaluate the diaphragm function. On US assessment, it is observed that diaphragm thickness decreases over time in mechanically ventilated patients. Numerous studies have shown good correlation between US and the gold standard method for diaphragm function assessment, bilateral anterior magnetic phrenic stimulation (BAMPs).[6]

Most studies of diaphragmatic dysfunction have been conducted on patients in general intensive care unit. However, there is paucity of literature on VIDD in TBI patients. We hypothesized that diaphragmatic thickness fraction (DTF) would decrease over the period of 7 days of mechanical ventilation. Thus, the aim of the present study was to observe changes in diaphragmatic function occurring over a time period in TBI patients receiving invasive mechanical ventilation. The objective was to observe the changes in DTF measured on day 0 (day of admission in the NICU on invasive mechanical ventilation) and then serially on days 3, 5, and 7. Other objectives of the study were to observe the changes in diaphragmatic excursion (DE) over a period of 7 days on pressure support ventilation (PSV) of 12 cm H_2O and to correlate the duration of hospital stay and days to wean with day 1 and 7 of DE and DTF. The rationale behind our objectives were to see if there is any association between diaphragmatic changes with overall prognosis in a mechanically ventilated TBI patient.

Methods

The study was conducted at the NICU of a level 1 trauma center after obtaining approval from the institute's ethics committee. Written informed consent was obtained from the patient's next of kin. Patients between the age of 18 and 65 years and suffering from TBI in whom mechanical ventilation was initiated within the last 24 hours were included in the study. Patients with spine injury, preexisting neuromuscular disor-

ders, history of chronic obstructive pulmonary disease (COPD), history of major thoracic and abdominal trauma or surgery, and pregnant patients were excluded from the study.

As a protocol, ventilation was initiated using the volume control ventilation (VCV) mode with tidal volume set at 8 mL/kg body weight, positive end-expiratory pressure (PEEP) of 5 cm H_2O, and respiratory rate of 14/min. These settings were changed as per individual patient requirements. Infusion of midazolam at 0.02 to 1 mg/kg/h from the initiation of ventilation was started. US assessment of diaphragm function was done in the supine position, during daily sedation interruption, which in our study was defined as stopping of midazolam infusion for at least 6 hours before assessing the patient and when they were given a spontaneous breathing trial with a pressure support of 12 cm H_2O and PEEP of 5 cm H_2O. Those who were not fully conscious were given inspiratory hold to measure the plateau pressure to rule out lung-related pathology as per our institutional protocol, while US measurements of all the study patients were done when the patients were breathing spontaneously. The US assessment of diaphragmatic function was done on days 0, 3, 5, and 7 of NICU admission. A 7- to 13-MHz linear array transducer probe (US machine SonoSite M-Turbo) was placed at the eighth or ninth intercostal space on the anterior axillary line and the zone of apposition was identified. The diaphragm was identified in the B mode of US by its characteristic three-layered appearance (►Fig. 1). A hypoechoic muscle layer sandwiched between two hyperechoic layers (parietal pleura and peritoneum). Diaphragm thickness was measured from the center of the pleural line to the center of the peritoneal line, at the zone of apposition between the eighth and ninth intercostal spaces on the right side in the midaxillary line. The measurement was done at end expiration (T_E) and at maximal inspiration (T_I). The measurements were taken three times consecutively and then averaged. The thickness fraction was calculated as $(T_I - T_E/T_E) \times 100$. The DE was measured using 1- to 5-MHz
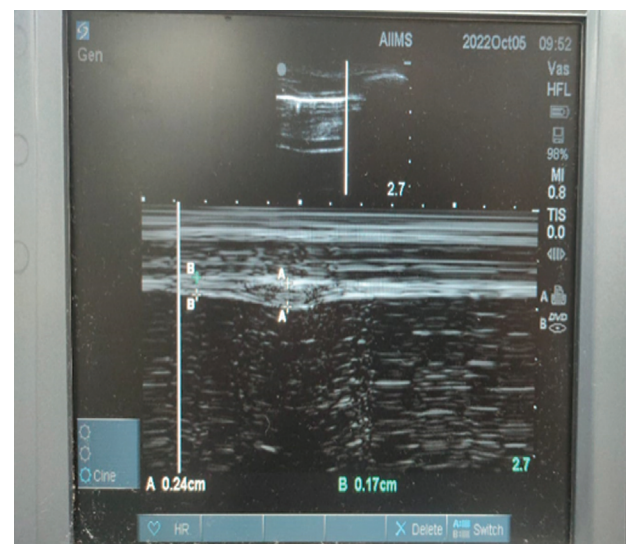

Fig. 1 The diaphragm is identified as the hypoechoic layer between two hypoechoic layers. Point A represents maximal inspiration (T_I) and B represents end expiration (T_E).
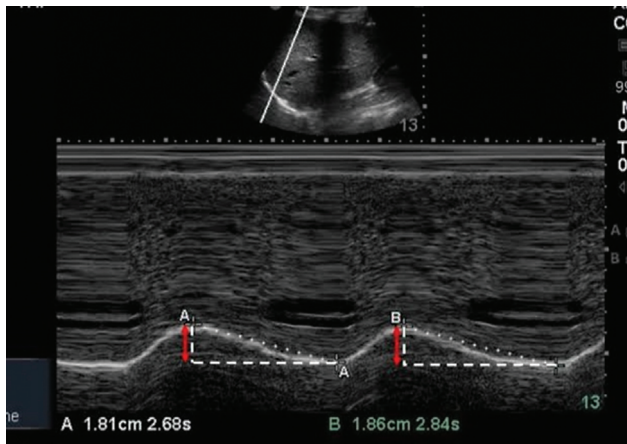
Fig. 2 The diaphragmatic excursion measured as the height of maximal inspiration.

phased array US transducer. The transducer was placed subcostal in the right midclavicular line. The DE was measured in the M mode using a transhepatic beam directed perpendicular to the diaphragm. It was measured as the maximal height of inspiration in M mode (►**Fig. 2**). Variables including patient demographics, time of injury and NICU admission, GCS, vital signs, and duration of hospital stay were also recorded. Long hospital stay in our study was defined as more than 20 days of hospital stay,[7] while late weaning was defined as weaning after 1 week.[8]

All patients were treated according to standard ICU protocol, which included antibiotic prophylaxis, DVT prophylaxis, antiedema measures for head injury patients, and mechanical ventilation. Feeding was initiated within 48 hours of injury via nasogastric tube whenever it seemed feasible, in the form of boluses every 2 hourly optimizing caloric needs of 25 to 30 kcal/kg/d and protein of 1.2 g/kg/d. Both chest and limb physiotherapy was provided to all patients in our study group.

Statistical Methods: Since there was no previous study available in this context, ours is a pilot study for which we enrolled 20 patients in each group with respect to 20 days of hospital stay. Statistical analysis was done using SPSS 22.0, and R environment ver.3.2.2, Microsoft word, and excel were used to generate graphs and tables. Descriptive and inferential statistical analysis was performed. Continuous measurements were presented as mean $\pm$ SD (minimum–maximum) and results on categorical measurements were presented in number percentage. Student's t-test (two tailed, independent) was used to find the significance of the study parameters on continuous scale between two groups (intergroup analysis) on metric parameters. Leven's test for homogeneity of variance was performed to assess the homogeneity of variance. Paired t-test was used to test the null hypothesis that the average of the differences between a series of paired observations is zero. Chi-squared/Fisher's exact test was used to find the significance of the study parameters on the categorical scale between two or more groups. Fisher's exact test was used when cell samples were small. Pearson's correlation between study

variables was performed to find the degree of relationship. Two percent change in DTF as well as DE was considered significant. A p value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

Forty patients with a mean age of 35.2 ± 12.9 years (39 males and 1 female) were evaluated. Thirty-three patients had severe TBI, 6 patients had moderate TBI, and 1 patient had mild TBI. Surgical intervention in the form of decompressive craniotomy/craniectomy was performed in 32 patients. The average duration of hospital admission was 19.82 ± 19.19 days (interquartile range [IQR]: 4–121). The demographic data and patient profile are depicted in ►**Table 1**.

Mean DTF at days 0, 3, 5, and 7 were 33.58 ± 10.08, 33.4 ± 9.76, 32.32 ± 8.36, and 31.65 ± 8.23, respectively. Changes in DTF was statistically significant on day 7 with p value of 0.040.

Mean DE at days 0, 3, 5, and 7 was 9.61 ± 3.99, 9.02 ± 3.46, 8.87 ± 2.63, and 8.56 ± 2.74, respectively. Changes in DE over days 3, 5, and 7 were all statistically significant ($p < 0.001$).

We found no significant correlation between DTF and hospital stay ($p > 0.05$). Similarly, no statistically significant correlation between DE and hospital stay was established ($p > 0.05$). The correlation analysis between DE and hospital stay as well as DE and days of weaning was also applied where we got no significant correlation between DE and hospital stay as well as DE and days of weaning ($p > 0.05$).

The mean hospital stay among our study group was 20 ± 19.19. The mean DTF at days 0, 3, 5, and 7 was 31.29 ± 9.17, 30.88 ± 8.24, 31.14 ± 6.72, and 32.83 ± 7.59, respectively, when hospital stay was short (<20 days), while the mean DTF was 37 ± 10.69, 37.19 ± 10.86, 33.88 ± 10.14, and 30.31 ± 8.95 for days 0, 3, 5, and 7, respectively, when hospital stay was long (>20 days). When both the groups were compared, a statistically significant difference between the two groups at days 0 and 3 ($p = 0.079$ and 0.044, respectively) was seen. The presenting DTF in. the patients with prolonged hospital was higher than those with shorter duration of hospital stay, although not statistically significant ($p = 0.079$).

The mean DE at days 0, 3, 5, and 7 was 9.47 ± 3.45, 8.78 ± 2.96, 8.96 ± 1.98, and 8.61 ± 1.91, respectively, when hospital stay was short, while the mean DE was 9.82 ± 4.81, 9.39 ± 4.19, 8.76 ± 3.35, and 8.51 ± 3.52 for days 0, 3, 5, and 7, respectively, in patients who had prolonged hospital stay. There was no statistically significant difference in DE among them at various time points.

The mean DTF at days 0, 3, 5, and 7 was 36.33 ± 6.87, 35.75 ± 5.51, 33.75 ± 5.41, and 34.5 ± 6.79, respectively, in patients who were weaned early (within 7 days), while the mean DTF at days 0, 3, 5, and 7 was 31.86 ± 11.17, 34.21 ± 9.81, 32.14 ± 9.79, and 29.86 ± 7.81, respectively, when weaning was delayed (>7 days). The data are represented in ►**Fig. 3**. When the mean DTF between early and delayed weaning was compared, no statistically significant differences was observed at days 0, 3, 5, and 7. Although not

Table 1 Baseline demographic characteristics of the patients

Demographic characteristics					
Age	18–30 y		31–50 y		51–65 y	
	16		19		5	
Gender	Male		Female			
	39		1			
Type of bleed	Multiple	SDH	EDH	Depressed fracture	Contusion	ICH
	13	11	3	5	5	2
Surgical decompression	Yes		No			
	32		8			
GCS on arrival	3–8 (severe TBI)		9–12 (moderate TBI)		13–15 (mild TBI)	
	33 (82.5%)		6 (15%)		1 (0.025%)	
M score	1	2	3	4	5	6
	1 (2.5%)	6 (15%)	4 (10%)	7 (17.5%)	18 (45%)	4 (10%)
Tracheostomy	Yes		No			
	24		16			
Hospital stay	<20 d		>20 d			
	24		16			
Weaning	<7 d		>7 d			
	14		26			
Outcome	Survival		Death			
	29		11			
GCS (group)	Early weaning		Late weaning		CI	p value
Early vs. late	7.86 ± 2.44		6.27 ± 1.78		−3.3018 to 0.1218	0.067

Abbreviations: CI, confidence interval; EDH, extradural hemorrhage; GCS, Glasgow coma scale; M score, motor score (GCS); SDH, subdural hemorrhage; TBI, traumatic brain injury.
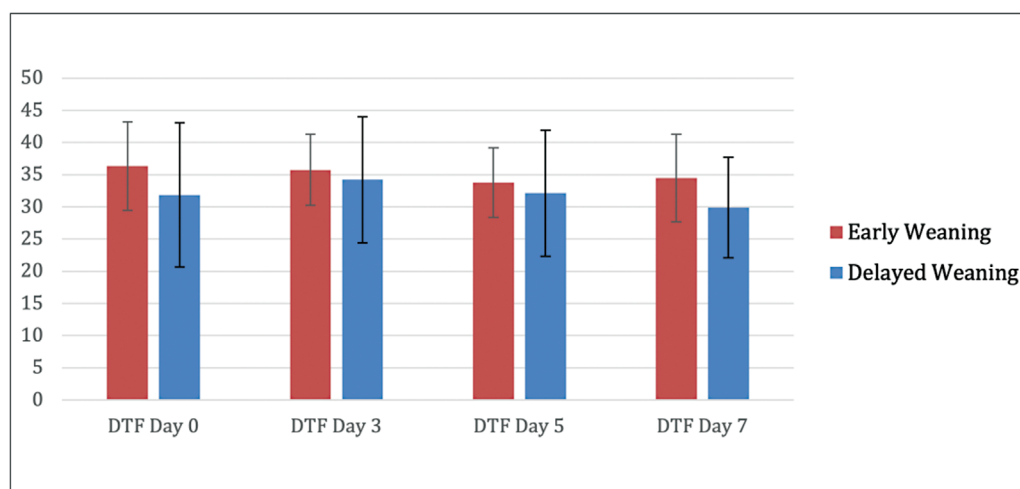

Fig. 3 Comparison of diaphragmatic thickness fraction (DTF) between patients who were weaned early (<7 days) and those who were weaned late (>7 days). Data are represented as mean ± standard deviation (SD).

statistically significant ($p = 0.246$), the presenting DTF was greater (36.33 ± 6.87) in the early weaning group as compared with the delayed weaning group. On intragroup analysis, a significant difference was observed in DTF at day 5 in comparison to day 0 ($p = 0.008$) in the early weaning group. Similar results were not seen in the delayed weaning group.

In the early weaning group, the mean DE at days 0, 3, 5, and 7 was 10.93 ± 2.66, 10.13 ± 2.28, 9.53 ± 1.91, and 9.23 ± 1.73, respectively. The mean DE at days 0, 3, 5, and 7 for the delayed weaning group was 9.09 ± 3.81, 8.89 ± 3.11, 8.54 ± 2.74, and 8.19 ± 2.73, respectively. When the mean DE from both groups were compared, significant differences
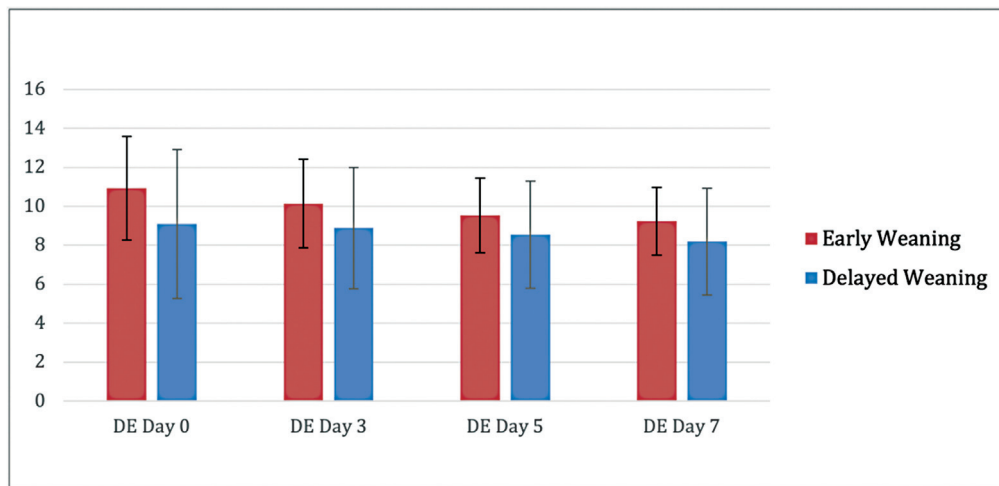
Fig. 4 Comparison of diaphragmatic excursion (DE) between patients who were weaned early (<7 days) and those who were weaned late (>7 days). Data are represented as mean ± standard deviation (SD).

were not observed. The comparison is represented in graphical form in ►**Fig. 4**. Further, on intragroup analysis, statistically significant changes in DE were observed at days 3, 5, and 7 in relation to day 0 ($p = 0.046$, 0.030, and 0.014, respectively) in the early weaning group. Similar results, however, were not obtained from the delayed weaning group.

We also divided the patients based on DTF ≤25 or ≥25% and observed their association with days of weaning as well as hospital stay. We observed no significant differences in duration of hospital stay ($p = 0.932$) among the respective groups. Ninety percent ($N = 9$) of patients with DTF ≤ 25% got weaned after 1 week, while 55.6% ($N = 15$) of patients with DTF >25% got weaned after 1 week. The difference was statistically not significant ($p = 0.065$).

Discussion

In our prospective observational study, we found that in TBI, changes in DTF were significant on day 7, while changes in DE were significant over days 3, 5, and 7 of admission. We were unable to establish any significant correlation between DTF or DE with hospital stay or days of weaning or vice versa.

Sonographic assessment of respiratory muscle like the diaphragm is a newer concept for predicting weaning in a neurosurgical ICU. The basic idea behind assessing the dynamics of the diaphragm is the mechanical ventilation-induced diaphragmatic inactivity, which leads to wasting of diaphragmatic muscle fibers, which ultimately leads to muscle atrophy as well as diaphragmatic dysfunction.[9] Goligher et al studied 96 mechanically ventilated patients and found that right hemidiaphragm thickness measurement is highly reproducible and over the first week of ventilation, diaphragm thickness decreased by more than 10% in 47 (44%), was unchanged in 47 (44%), and increased by more than 10% in 13 (12%) patients. They also found that contractile activity decreased with increasing ventilator driving pressure and controlled ventilator modes. They concluded that US measurements of the right hemidiaph-

ragm thickness at clinically relevant inspiratory volumes can be reliably employed to monitor diaphragm thickness, activity, and function during mechanical ventilation.[10] In our study as well, a decrease in DTF was noted over 7 days of ventilation and it was more decreased in patients who required mechanical ventilation for longer duration (>7days). Farghaly and Hasan studied the role of diaphragm US as a method to predict extubation outcome in mechanically ventilated patients. They concluded that US evaluation of diaphragmatic parameters such as excursion, thickness at end inspiration, and diaphragm thickness excursion could be good predictors of extubation outcome in patients who passed spontaneous breathing trial.[11] Our findings were also similar to theirs; although the difference was not statistically significant, it was clinically significant as 90% of patients with DTF ≤ 25% required prolonged ventilation, while only 55.6% of patients with DTF >25% had delayed weaning. Qian et al, in a meta-analysis, studied the correlation of US assessment of diaphragm dysfunction and weaning outcome. They concluded that despite of heterogeneity among studies, DTF and DE could be used to predict weaning outcomes; however, we were unable to establish any significant corelation.[12] The reasons for nonlinear correlation between DTF or DE with weaning and days of hospitalization can be the presence of other associated injuries, fluid balance, sepsis, multi-organ failure, deep vein thrombosis, and iatrogenic injuries (pneumothorax, postventricular drainage meningitis).[13]

In our study, we observed a decrease in DTF as well as DE over the period of 7 days of elective ventilation following TBI. This trend was like the findings by Ali and Mohamad, who studied 60 mechanically ventilated patients and compared them with 20 healthy nonmechanically ventilated individuals. Diaphragm thickness and excursion were measured daily for 14 days or until extubation or death. They observed significant decrease in the DTF and mean DE with increased length and duration of mechanical ventilation.[14] Grosu et al observed a reduction in diaphragmatic thickness by 6% per day in mechanically ventilated patients.[15] Similar finding of

reduction in diaphragmatic thickness was observed in a study conducted by Zambon et al.[3] Schepens et al studied the effect of mechanical ventilation on the diaphragm. In this study, 54 mechanically ventilated patients were enrolled, and daily US assessment of the diaphragm was done. They concluded that diaphragm atrophy as assessed by US occurs quickly in mechanically ventilated patients. The rate of atrophy proportionally increases with increased duration of mechanical ventilation.[16] Compared with DE where decrease was significant over the period of 7 days, decrease in DTF was significant only on day 7, which we could not explain. It may be due to operator bias or difference in sensitivity of two different frequency probes used.

The strength of this study was that this is the first prospective study conducted to measure diaphragmatic parameters in TBI. There are a few limitations of our study. It was a single-center study with a small sample size, and injury or severity-specific variability was not ascertained due to a small sample size. Small number of patients in prolonged and failed weaning may have underestimated the differences. Due to smaller sample size, individual trigger sensitivity for each patient group could not be tested. There is a difference in management of head injury on an individual basis. Intraoperative as well as postoperative complications were not taken into consideration. Baseline electrophysiological testing to rule out preexisting neuropathy or myopathy was not done. A single US machine was used to assess both DTF and DE, which contributed to time lag between the measurements. Malnutrition, which can be preexisting or because of critical illness, cannot be ruled out; other parameters that can change the thickness of the diaphragm were not taken into consideration. Similarly, ventilator-induced lung injury and diaphragmatic dysfunction could not be ruled out. In conclusion, decrease in DTF and DE over the period of 7 days was observed with a significant decrease occurring on the seventh day following TBI.

Conflict of Interest
None declared.

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