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ORIGINAL ARTICLE

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Diaphragm atrophy during invasive mechanical ventilation is related to extubation failure in preterm infants: An ultrasound study

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Abstract

Background: Diaphragm dysfunction is associated with poor outcomes in critically ill patients. Ventilator-induced diaphragmatic dysfunction (VIDD), including diaphragm atrophy (DA), is poorly studied in newborns. We aimed to assess VIDD and its associations in newborns.

Methods: Single-center prospective study. Diaphragm thickness was measured at end-inspiration (TDI) and end-expiration (TDE) on the right midaxillary line. DA was defined as decrease in TDE ≥ 10%. Daily measurements were recorded in preterm newborns on invasive mechanical ventilation (IMV) for ≥2 days. Clinical characteristics of patients and extubation failure were recorded. Univariate analysis, logistic regression, and mixed models were performed to describe VIDD and associated factors.

Results: We studied 17 patients (median gestational age $27^{0/7}$ weeks) and 22 IMV cycles (median duration 9 days). Median TDE decreased from 0.118 cm (interquartile range [IQR] 0.094–0.165) on the first IMV day to 0.104 cm (IQR 0.083–0.120) on the last IMV day ($p = .092$). DA occurred in 11 IMV cycles (50%) from 10 infants early during IMV (median: second IMV day). Mean airway pressure (MAP) and lung ultrasound score (LUS) on the first IMV day were significantly higher in patients who developed DA. DA was more frequent in patients with extubation failure than in those with extubation success within 7 days (83.3 vs. 33.3%, $p = .038$).

Conclusions: DA, significantly associated with extubation failure, occurred in 58.8% of the study infants on IMV. Higher MAP and LUS at IMV start were associated with DA. Our results suggest a potential role of diaphragm ultrasound to assess DA and predict extubation failure in clinical practice.

KEYWORDS
diaphragm atrophy, extubation failure, infant, ventilator induced diaphragm dysfunction

Preliminary results of this study were presented as a poster at the European Academy of Pediatric Societies (EAPS) Congress held in Barcelona on 7–11 October 2022.

1 | INTRODUCTION

Although noninvasive ventilation and less invasive surfactant administration are increasingly used in neonatal units, invasive mechanical ventilation (IMV) is still commonly administered to preterm infants.[1] Prolonged IMV is associated with mortality and morbidities, including sepsis, bronchopulmonary dysplasia (BPD) and neurodevelopmental impairment.[2–4]

In newborns, the diaphragm represents the main inspiratory muscle, and there are structural and functional physiological differences compared to older children and adults: the highly compliant rib cage, the horizontal position of the ribs (which limits the role of the accessory muscles of respiration), the smaller zone of apposition of the diaphragm and its poor functional reserve due to the paucity of fatigue-resistant muscle fibers.[5] IMV leads to a rapid development of diaphragmatic weakness due to the onset of muscle atrophy and contractile dysfunction. This condition has been defined as ventilator-induced diaphragmatic dysfunction (VIDD) and has been increasingly studied also considering its potential complications. The development of VIDD has been demonstrated in animals, adults, and children. It has been suggested that VIDD may be secondary to proteolysis, contractile dysfunction, and reduced protein synthesis.[6] VIDD has been associated with adverse outcomes in adults and children, including extubation failure, prolonged postextubation noninvasive positive pressure ventilation and mortality.[7,8] Diaphragm atrophy (DA, thickness reduction ≥10% compared to baseline) is one of the manifestations of VIDD. In children and adults undergoing IMV, the development of VIDD and DA was associated with adverse outcomes such as extubation failure, increased mortality, and prolonged hospital admission.[8–12]

There is paucity of studies about VIDD in newborns: authors mainly investigated on the role of diaphragm ultrasound for the prediction of successful extubation [13,14] and only one recent study assessed the development of DA in preterm infants born <28 weeks but did not report DA-associated outcomes.[15]

We therefore aimed to describe the changes in diaphragm thickness during IMV and the prevalence and associations of DA, particularly regarding the relationship between DA and extubation failure.

2 | MATERIALS AND METHODS

This was a prospective observational study at a single level III neonatal intensive care unit (NICU) at Fondazione Policlinico Gemelli IRCCS in Rome (Italy) between February 2021 and February 2022. We studied preterm infants born <37 weeks of gestation who required IMV for at least 48 h during their NICU admission. Infants with chromosomal abnormalities, major malformations, gestational age <23 weeks, need for palliative care were excluded. Demographic information, including gestational and postnatal age, sex, length, weight, comorbid conditions, details about nutrition, and drugs were recorded. Extubation failure was defined as the requirement for reintubation within the 7 days following extubation due to the abovementioned criteria (need for further surfactant doses, severe respiratory acidosis, or apnea). The requirement for noninvasive ventilation (continuous positive airway pressure [CPAP] or nasal intermittent mechanical ventilation) following extubation was also recorded.

The study was approved by the local Ethics Committee (protocol number 0050044/20), and written informed consent was obtained from the legal guardians of each infant. The decision to intubate and start endotracheal IMV was based on the need for surfactant administration (FiO2 ≥ 0.30 despite adequate noninvasive ventilation, diagnosis of RDS), on the development of respiratory acidosis (pH < 7.20, pCO2 > 60–65 mmHg), or severe apnea.[16–18] After surfactant administration, infants with adequate respiratory drive were extubated within 30 min and put on nasal CPAP; infants with persisting FiO2 ≥ 0.40, respiratory acidosis or severe apnea were kept on IMV until extubation criteria were met. Less invasive surfactant administration is not routinely used at our Institution. For other IMV indications, infants were extubated if mean airway pressure (MAP) < 8 cmH20, FiO2 < 0.30, good respiratory drive were evident. While on IMV, SatO2 target was 90%–94%, pH was kept between 7.25 and 7.35, pCO2 was maintained between 45 and 60 mmHg as per local protocols. High-frequency oscillatory ventilation (HFOV) with volume guaranteed (VG) was preferred for infants born <28 weeks of gestation, for those with air leak or lung hypoplasia; synchronized intermittent mandatory ventilation (SIMV) with VG could also be used at discretion of the attending physician. Sedation was provided to minimize discomfort, and neonatal pain scales were routinely used to titrate sedative dose as per local guidelines. Remifentanyl is the drug of choice at our Institution thanks to its short half-life and low toxicity profile. The drug is administered by i.v. continuous infusion at doses between 0.01 and 0.5 mcg/kg/min. In some cases, fentanyl is used at discretion of the attending physician, and the drug is infused at a rate of 1–5 mcg/kg/h. Dexmedetomidine is sometimes used upon clinician's judgment in infants >28 weeks postmenstrual age by continuous i.v. infusion at 0.1–0.5 mcg/kg/h.

Lung ultrasound was performed as clinically indicated depending on the availability of skilled operators, and lung ultrasound score (LUS) was calculated as previously reported.[19]

Diaphragm ultrasound was randomly conducted by two physicians (S. N., N. S.), using a 12 MHz linear probe (Logiq E9, General Electrics) with a resolution limit of 0.01 mm. Infants were kept in the supine position, and the probe was longitudinally applied on the right midaxillary line (diaphragm apposition zone). We chose to record measurements on the right hemidiaphragm thanks to the higher repeatability compared to the left hemidiaphragm.[8] Diaphragm thickness at end-inspiration (DTI) and end-expiration (DTE) were recorded, and diaphragm thickening fraction was calculated as (DTI − DTE)/DTE as previously reported, see Figure 1.[11,20] DA was defined as ≥10% decrease in DTE.[9]

Measurements were performed daily while intubated. Extubation failure was defined as the need for reintubation and IMV start according to the abovementioned criteria (need for further surfactant doses, respiratory acidosis, severe apnea).

Results are reported as percentages, mean (standard deviation) for normally distributed variables and as median (interquartile range, IQR) for nonnormally distributed variables. Univariate analysis (T-test, Mann–Whitney test, chi-squared test as appropriate) were used to

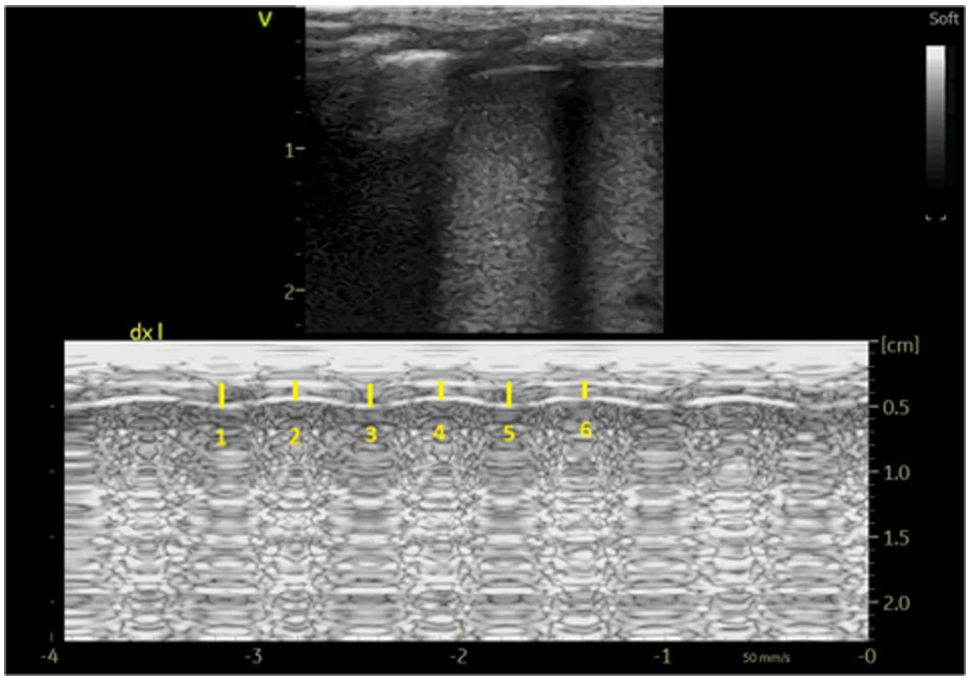

FIGURE 1 Diaphragm ultrasound in M-mode showing the TDI (average value of measures number 1, 3, and 5) and TDE measurements (average value of measures number 2, 4, and 6). The probe was longitudinally applied on the right midaxillary line (diaphragm apposition zone).

explore associations of DA. We used logistic regression to assess the relationship between patient characteristics and DA. Risk factors for DA with a $p < .20$ on univariate analyses were entered into multivariate logistic regression, and the best model was chosen based on the Hosmer–Lemeshow and the Nagelkerke tests. Linear mixed-effect models were used to explore the effect of days on IMV on DTE as well as other variables. The intraclass correlation coefficient was calculated to assess the reproducibility of the method: 10 randomly selected measurements taken by two operators (S. N. and N. S.) were considered for this calculation.

SPSS (version 23.0, IBM) was used to compute statistics.

At the time of the study conceptualization, there were no studies with the same objectives, we initially considered this as a pilot study without a formal sample size calculation. We performed a post hoc power analysis based on the occurrence of DA in the groups of infants with versus without extubation failure.

3 | RESULTS

Seventeen patients were enrolled and 22 IMV cycles were assessed in the study period: demographics and clinical characteristics of patients according to the development of DA are shown in Table 1. The median duration of IMV cycles was 9 days (IQR 3–21); the median day of life at IMV start was 6.5 days (IQR 1–17). Ten cycles were recorded in SIMV + VG, 12 in HFOV + VG.

To assess interobserver variability, 10 randomly selected subjects were identified. The population mean for the two assessors was: for DTE 0.126 cm (95% confidence interval 0.02) with a mean difference of 0.017 and an intraclass correlation coefficient of 0.863 (95% confidence interval 0.456–0.939), indicating good agreement; for DTI 0.174 cm (95% confidence interval 0.03) with a mean difference of 0.011 and an intraclass correlation coefficient of 0.919 (95% confidence interval 0.759–0.973), indicating good agreement.

DTE on the first IMV day was 0.118 cm (IQR 0.094–0.165); DTE on the last IMV day was 0.104 cm (IQR 0.083–0.120). Mean daily percentage change in DTE was −2.5% (SD 15.47) during the first 2 days of IMV. DTE showed a nonsignificant decrease over time on IMV, with a regression coefficient of −0.004 (95% confidence interval −0.010 to 0.001, $p = .092$), as depicted in Figure 2 (in this model, the effect of time on IMV on DTE was tested). We then tested other variables in the mixed model analysis: the most informative model (Bayesian information criterion 39.03) included gestational age at birth, age at IMV cycle, duration of the IMV cycle, sepsis as fixed effects, and individuals as random effects. No significant associations between these variables and DTE change was found (all $p > .05$, see Supporting Information S1: Table 1).

DA was evident in 11/22 IMV cycles (50%) from 10/17 patients (58.8%) anytime during the IMV cycle, whereas DA between the first and the last day of the IMV cycle was found in 8/22 (36%) of the IMV cycles. DA occurred early during the IMV course (median: 2nd IMV day; IQR 1–3 days). In seven cycles, DA was evident on the second IMV day, in other three cycles during the third IMV day, in another cycle during the fifth IMV day. Associations between DA and clinical characteristics of patients are shown in Table 1: only MAP and LUS on the first IMV day were significantly different between groups,

TABLE 1 Clinical characteristics of patients and associations of DA (univariate analysis).

	DA (*n.* 10 patients)	No DA (*n.* 7 patients)	*p* Value
Demographics and antenatal characteristics			
Gestational age, weeks	$26^{6/7}$ ($24^{6/7}$-$28^{6/7}$)	$27^{0/7}$ ($26^{1/7}$-$33^{6/7}$)	0.315
Birth weight, g	773 (648–1391)	820 (710–2010)	0.536
Male sex, *n* (%)	7 (70.0)	3 (42.8)	0.350
SGA, *n* (%)	2 (20.0)	2 (28.6)	1.000
Anhydramnios, n (%)	3 (30.0)	1 (14.3)	0.569
Singletons, *n* (%)	5 (50.0)	4 (57.1)	1.000
Antenatal steroids, *n* (%)	2 (20.0)	4 (57.1)	0.302
Chorioamnionitis, *n* (%)	0 (0)	2 (28.6)	0.200
Clinical characteristics			
Birth asphyxia, *n* (%)	1 (10.0)	2 (28.6)	0.537
EOS, *n* (%)	1 (10.0)	2 (28.6)	0.288
LOS, *n* (%)	6 (60.0)	3 (42.9)	0.238
Anytime sepsis, *n* (%)	6 (60.0)	5 (71.4)	0.644
Sepsis during first MV day, *n* (%)	3 (30.0)	4 (57.1)	0.350
Patent ductus arteriosus during first MV day, *n* (%)	4 (40.0)	1 (14.3)	0.153
N. of surfactant doses, median (IQR)	2 (1–3)	1 (0–2)	0.070
NIV days, mean (SD)	45 (34)	37 (36)	0.668
Oxygen hours, median (IQR)	756 (269–1908)	504 (2–864)	0.230
Nihil per os days, median (IQR)	4 (2–7)	2 (1–3)	0.230
Protein intake (g/kg/day) during the MV course, mean (SD)	2.4 (0.9)	3.1 (1.5)	0.252
Energy intake (kCal/kg/day) during the MV course, mean (SD)	66.5 (26.2)	78.0 (36.4)	0.457
Number of sedative drugs during MV, median (IQR)	1 (1–2)	2 (1–2)	0.740
Age (days) on first MV day, mean (SD)	8 (9)	8 (7)	0.966
Weight (g) on first MV day, median (IQR)	890 (713–1328)	820 (720–2010)	0.887
LUS on first MV day, mean (SD)	**8.5 (3.7)**	**3.5 (1.9)**	**0.040**
Remifentanyl highest dose during the MV cycle (mcg/kg/min), median (IQR)	0.21 (0.05–0.48)	0.18 (0.09–0.65)	0.536
HFOV + VG on MV Day 1, *n* (%)	7 (70.0)	3 (42.9)	0.350
MAP (cmH_20) on first MV day, mean (SD)	**13.3 (3.1)**	**10.2 (1.7)**	**0.047**
DTI (mm) on first MV day, median (IQR)	0.15 (0.11–0.20)	0.11 (0.10–0.21)	0.364
DTE (mm) on first MV day, median (IQR)	0.12 (0.09–0.16)	0.09 (0.08–0.17)	0.133
DTF on first MV day, median (IQR)	24.2 (0–29.1)	23.5 (22.2–40.0)	0.417

Note: Bold values indicate statistically significant differences.

Abbreviations: DA, diaphragm atrophy; DTE, Diaphragm thickness at end-expiration; DTF, diaphragm thickening fraction; DTI, Diaphragm thickness at end-inspiration; EOS, early onset sepsis; HFOV, high-frequency oscillatory ventilation; IQR, interquartile range; LOS, late onset sepsis; LUS, lung ultrasound score; MV, mechanical ventilation; NIV, noninvasive ventilation; SGA, small for gestational age; VG, volume guaranteed.

being higher in patients who developed DA. Considering the occurrence of DA in the groups of infants with versus without extubation failure, our study has a power of 68.6% to detect differences with $p \leq .05$.

There was no significant difference in neonatal complications (BPD, NEC grade 3–4, intraventricular haemorrhage grade ≥3, periventricular leukomalacia, retinopathy of prematurity stage ≥3) and in days of hospital admission between infants with DA compared with those without DA (all $p > .05$). Extubation failure within 7 days was evident after 6/22 (27.3%) IMV cycles. DA (anytime during the IMV cycle) was more frequent in patients with extubation failure than in those with extubation success within 7 days (83.3 vs. 33.3%, $p = .038$).

A logistic regression analysis run to assess predictors of DA found no significant association. The model included DTE, MAP, remifentanil dose on the first IMV day and anhydramnios; the Hosmer–Lemeshow value of the model was 0.784, indicating a good fit (Table 2). The Nagelkerke R^2 value of the model was 0.672.

4 | DISCUSSION

The main findings of this prospective observational study were that DA frequently occurred in infants on IMV, and that DA was associated with increased risk for extubation failure.

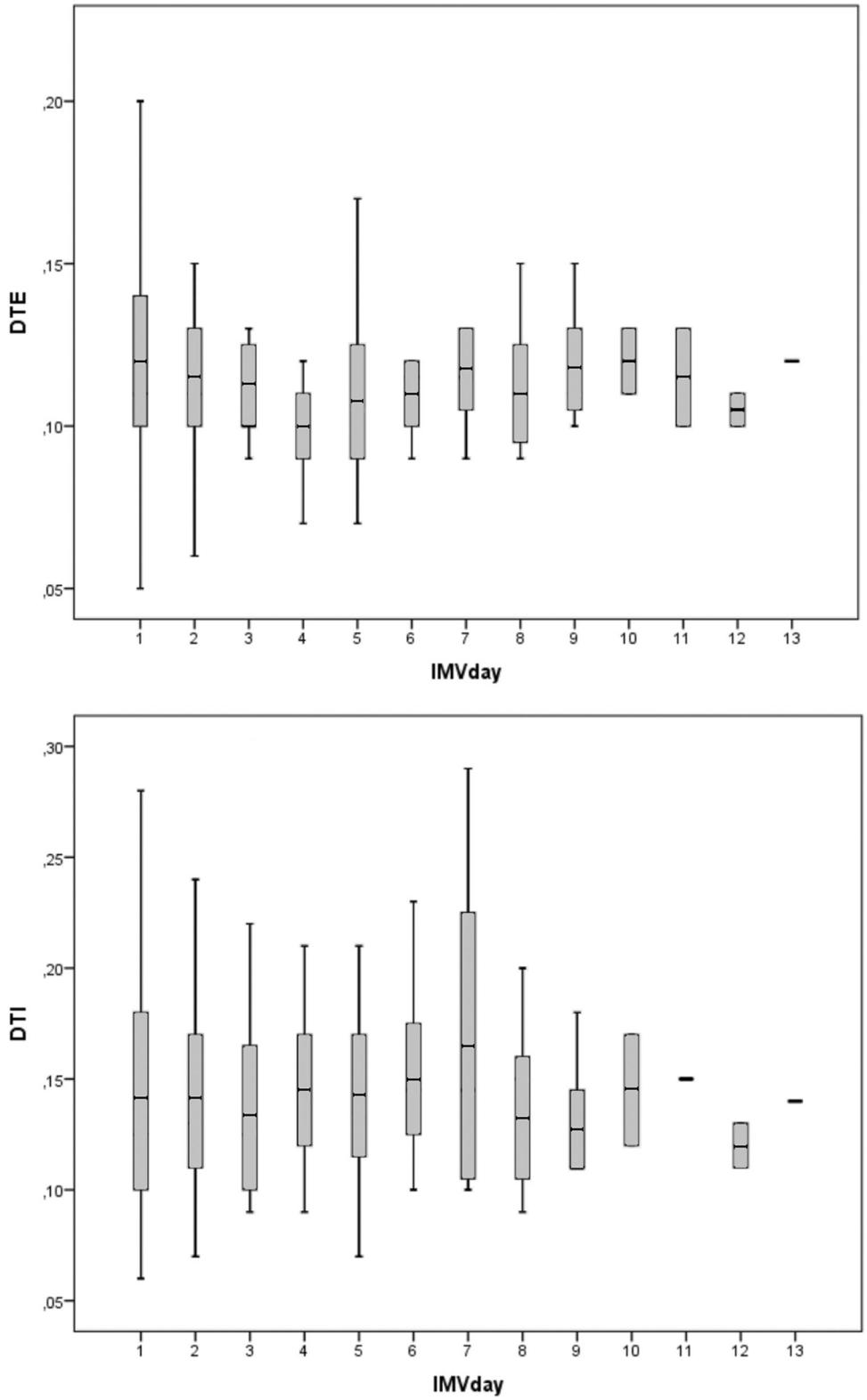

FIGURE 2 Upper panel—DTE (mm) mean, SD values, lowest and highest value over days on invasive mechanical ventilation (IMV); panel B DTI (mm) mean, SD, lowest and highest values over days on IMV. The number of patients assessed during each IMV day was 22, 22, 16, 15, 11, 8, 8, 7, 3, 2, 2, 2, 1, respectively.

TABLE 2 Logistic regression analysis assessing predictors of DA.

	Odds ratio	95% confidence interval	*p* Value
DTE on the first IMV day, mm	15.650	0.005–67.463	.193
MAP on the first IMV day, cmH20	1.880	0.797–4.435	.150
Remifentanil highest dose on the first IMV day, mcg/kg/min	0.003	0.001–11.748	.409
Anhydramnios	6.722	0.577–78.323	.128

Abbreviations: DA, diaphragm atrophy; IMV, invasive mechanical ventilation; MAP, mean airway pressure.

DA and VIDD have been reported in 41% of adults 47% of children undergoing IMV and has been associated with adverse outcomes.[8,10,21,22] In a recent study with 20 extremely preterm infants, 90% of them were found to have VIDD, however, the incidence of DA was not reported.[15] Moreover, the authors of this study only provided data on TDI and diaphragm thickening fraction (DTF) change but not on TDE change. In our experience, and based on pathophysiologic considerations, TDI reflects the individual's ability to contract the diaphragm and is therefore influenced by multiple factors such as sleep state, agitation (and level of sedation), time from last meal, drugs (i.e., caffeine). On the contrary, TDE represents the diaphragm trophism and could be less influenced by such factors; we reported changes in TDI, TDE, and DTF and also DA, which was found in 50% of the IMV cycles in preterm infants. Proposed risk factors for VIDD and DA in previous studies were an abnormally low inspiratory effort during IMV in adults [8] and a prolonged duration of IMV and elevated C-reactive protein levels in children.[12] We found significant associations between DA and higher LUS and MAP on the first day of IMV. Our observation that a higher LUS was associated with extubation failure confirms the results of a recent study in preterm infants.[23] Possible explanations for our findings could be that ventilation with higher MAP inhibits diaphragm contraction (thus facilitating the development of DA). It should be noted that we studied particularly sick preterm infants, in whom the process of diaphragm thinning could have started hours or days before intubation (i.e., due to inflammation and/or other factors): in fact, most patients had sepsis during IMV and many of them were twins and were born small for gestational age (SGA). It is important to note that other potentially important factors such as birth characteristics, age at IMV, nutritional practices, the type of ventilation, and the use of sedatives were not significantly associated with DA in our cohort. Our results did not confirm previous observations by Alonso-Ojembarrena et al.,[24] who recently reported a significant direct association between birth weight and increase in diaphragm thickness over time and the lack of association between days on IMV and diaphragm thickness. It is possible that differences in population characteristics, clinical practices, and importantly in the study design could explain these discrepancies.

HFOV may overdistend the lungs and create a mechanical disadvantage for the diaphragm. We used VG to overcome this issue, and indeed found no significant difference between HFOV and SIMV on the development of DA. However, this is only a speculation, and this study was not conceived to address this issue.

Regarding the consequences of VIDD/DA, in adults undergoing IMV the development of DA was associated with increased duration of IMV, hospitalization, and complications of acute respiratory failure (reintubation, tracheostomy, prolonged IMV).[8] In children, VIDD and DA have been associated with prolonged length of stay, and higher incidence of extubation failure and mortality.[11,12] Moreover, a decrease in thickness of the expiratory muscles was more pronounced in children who failed extubation.[22] There are few data available in the newborn population: two studies showed that infants with IMV weaning failure had significantly reduced diaphragm excursion compared to those with IMV weaning success.[13,14] Diaphragm excursion was calculated as the distance between the greatest caudal descent (at the end of inspiration) and the greatest cranial elevation (at the end of expiration) of the posterior third of the diaphragm. In our study, DA was associated with increased incidence of extubation failure, confirming previous observations in children. This association is not surprising since in newborns the diaphragm is the main inspiratory muscle and has poor functional reserve.[5] We cannot directly compare our results to those from previous studies on newborns for methodological reasons: Bhagat et al. measured diaphragm features only within 1 h from a planned extubation, whereas El Halim et al. did not describe the timing of diaphragm ultrasound assessments.[13,14] Mohsen et al. assessed diaphragmatic excursion and diaphragmatic thickness fraction in ventilated extremely preterm infants; they did not find significant differences in these parameters between infants with extubation success compared to those with extubation failure.[23] Only the lung ultrasound severity score was significantly lower in the successful group compared to failed group. However, the authors studied diaphragmatic contractility only once, during a spontaneous breathing trial with tracheal CPAP and just before extubation.

We performed diaphragm ultrasound every day during the IMV cycle starting from the first day, whereas the assessment of diaphragm excursion was not included in our study protocol. As in other age groups, extubation failure was more likely in infants developing DA, but no associations with other neonatal complications were found in our cohort. It is possible that the small sample size could have prevented us to find other significant associations. Furthermore, extubation failure within 7 days could have been influenced by other factors which might have occurred in this timeframe (i.e., the onset of sepsis).

Regarding the pathophysiology of VIDD/DA, previous studies proposed associations with increased proteolysis, reduced protein synthesis, and contractile dysfunction and highlighted the role of inflammation, mitochondrial dysfunction, and IMV-induced reactive oxygen species production.[6,11,12] Moreover, IMV is known to reduce

diaphragmatic force production and facilitates muscle atrophy. Other important factors could be age and the use of neuromuscular blockade and corticosteroids.[6] We did not use neuromuscular-blocking agents and rarely use systemic corticosteroids, particularly after repeated episodes of extubation failure and prolonged need for IMV. Hence, we cannot report on these associations in the neonatal population. Ultrastructural changes in diaphragm muscle fibers have been demonstrated in animal models but are difficult to confirm in humans.

This study has some limitations: first, the small sample size precludes firm conclusions, also considering that extubation outcome in premature infants might be influenced by multiple factors. Second, our study infants may not be representative of other populations, as many of them were twins, SGA, and had sepsis during the IMV course. Moreover, local practices about sedation and nutrition could be different compared to others. Furthermore, we studied preterm infants with very thin diaphragm, hence the margin of error could be high; however, as in other studies conducted among infants, the agreement between operators was good, and the measures of at least two respiratory cycles were averaged to minimize the risk of errors.

Finally, we used SIMV + VG or HFOV + VG based on clinician's judgment and were not able to include other ventilation modalities and compare them one another. Therefore, our findings should be replicated in other contexts to confirm the results.

In conclusion, in this observational study in preterm infants, the development of DA was demonstrated in 50% if the IMV cycles and was associated with extubation failure. Associations of DA were higher MAP and LUS on the first IMV cycle. Our data, if replicated in other contexts, suggests that the assessment of DA might be useful to find out patients at risk for extubation failure and that gentler ventilation strategies (i.e., with the lower possible MAP) might be useful in preventing DA.

AUTHOR CONTRIBUTIONS

Stefano Nobile: Conceptualization; investigation; writing—original draft; writing—review and editing; data curation; methodology; formal analysis. **Annamaria Sbordone**: Writing—original draft; investigation; methodology. **Nicola Salce**: Investigation; writing—original draft; methodology. **Maria Letizia Patti**: Investigation; writing—original draft. **Alessandro Perri**: Investigation; writing—original draft. **Simona Fattore**: Investigation; writing—original draft. **Giorgia Prontera**: Investigation; writing—original draft. **Lucia Giordano**: Investigation; writing—original draft. **Milena Tana**: Investigation; writing—original draft. **Giovanni Vento**: Writing—review and editing; supervision; validation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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