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Effects of caffeine on diaphragmatic activity in preterm infants

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Abstract

Background: Caffeine is the first-choice drug for the treatment for apnea of prematurity (AOP) in preterm infants and it has been reported that it improves the diaphragm activity. The aim of this study was to evaluate by ultrasound possible changes in diaphragm contractility and motility induced by caffeine.

Methods: We studied 26 preterm infants with gestational age ≤34 weeks treated with caffeine for the prevention or treatment of AOP. Diaphragmatic ultrasound was performed 15 min (T_0) before and 60 min (T_{60}) after the loading (20 mg/kg) or maintenance (5 mg/kg) dose of caffeine.

Results: Diaphragmatic excursion (DE) and thickness at the end of inspiration (DT-in) and expiration (DT-ex), as well as peak velocity of the excursion at the end of inspiration (DT-in) and expiration (DT-ex) increased after administration of both loading and maintenance dose of caffeine.

Conclusions: Ultrasounds confirmed that caffeine improves the activity of diaphragm in preterm infants improving its thickness, amplitude of excursions, and contraction velocity. These results are consistent with the effectiveness of caffeine in treating AOP and decreasing the risk of failure of noninvasive respiratory support in preterm infants with respiratory distress syndrome (RDS).

KEYWORDS
caffeine, diaphragm, echography, point-of-care, preterm infant, ultrasound

1 | INTRODUCTION

Apnea of prematurity (AOP) occurs in 85% of infants born <34 weeks of gestational age and its occurrence is inversely proportional to the degree of prematurity and interests almost all patients born <30 weeks or with a birth weight (BW) <1000 g.[1]

AOP can be elicited by immaturity of brain stem respiratory center, which causes a reduced or absent inspiratory effort (central apnea), an obstruction of the upper airways (obstructive apnea), or a combination of both mechanisms (mixed apnea).[2] Reduction of breath control leads to an interruption of the activity of inspiratory (i.e., diaphragm and intercostal muscles) and dilator respiratory muscles which combined with high compliance of the soft tissues may favor the collapse of the upper airways.[2] Although it is difficult to strictly correlate AOP with long-term outcomes in very preterm infants because they often have severe cocomorbidities, it has been reported that prolonged and recurrent hypoxemia and bradycardia secondary to AOP can be detrimental for their neurodevelopment.[2–4]

Caffeine is the first-choice drug for the treatment of AOP in preterm infants,[5] and it has been demonstrated that it is effective in decreasing the risk of extubation failure in the recovery phase of respiratory distress syndrome (RDS)[6] and bronchopulmonary dysplasia (BPD),[5] and that it improves the survival rate without neurodevelopmental disabilities at 18–21 months of age.[6–8]

Several studies have shown that caffeine acts both centrally, by competing with the inhibitory effect of adenosine on its receptors and increasing the sensitivity of the respiratory centers to CO_2,[9,10] and peripherally, by directly stimulating diaphragm activity.[11,12] The exact mechanism by which caffeine enhances diaphragmatic function is not fully understood. However, in addition to improving the central stimulation of the diaphragm, caffeine would enhance its activation and contractility by increasing the calcium concentration in the sarcoplasmic reticulum and the release of adrenaline from the adrenal glands.[13] These mechanisms could determine an increase of tidal volume and minute ventilation, reducing the need for mechanical ventilation, and the extubation failure rate.[14]

The increase of diaphragmatic electrical activity promoted by caffeine has been measured through electromyography and fluoroscopy, but few data are available on the effect of caffeine on velocity and contractile strength of the muscle.[11,15]

On the other hand, diaphragmatic ultrasound is a point-of-care diagnostic tool, able to measure the thickness of the diaphragm, amplitude, and velocity of its excursions,[16,17] allowing repeated noninvasive measurements suitable to assess the effects on this muscle of pharmacological treatment and respiratory supports.

Thus, the aim of our study was to evaluate the possible changes in diaphragm contractility and motility induced by caffeine administration in a cohort of preterm infants using a standard ultrasound method, such as M-Mode, and Tissue Doppler Imaging (TDI), an innovative ultrasound method.

2 | MATERIALS AND METHODS

This prospective observational study was carried out at the third level neonatal intensive care units (NICU) of Careggi University Hospital of Florence and "G. Martino" University Hospital of Messina, after the approval of local Ethics Committees.

The study involved preterm infants with gestational age ≤34 weeks, born from March to August 2022 who received caffeine for the prevention or treatment of AOP. Exclusion criteria were need for mechanical ventilation, intraventricular hemorrhage (IVH) >3° grade, major congenital malformations, chromosomal abnormalities, and haemodynamic instability.

2.1 | Caffeine therapy

Caffeine citrate (Peyona©; Chiesi Farmaceutici Spa) was given intravenously, through a peripheral or central venous catheter, or enterally, through a nasogastric tube, with a loading dose of 20 mg/kg (treatment started within 12 h of life) and a maintenance dose of 5 mg/kg (initiated 24 h after the loading dose).[18]

2.2 | Ultrasound evaluations

Infants involved in the study underwent ultrasound evaluation (Affiniti 70 G™; Philips) of the right hemidiaphragm (RD) using the liver to improve the acoustic window because, as previously reported, the presence of gas or food in the stomach and the lack of a precise anatomical reference can induce interference sounds with left hemidiaphragm visualization.[16,19]

The study of diaphragmatic dynamics was performed 15 min (T_0) before and 60 min (T_{60}) after the loading or maintenance dose of caffeine. Measurements of diaphragmatic thickness (DT) at the end of inspiration (DT-in) and expiration (DT-ex) were performed using

TABLE 1 Clinical characteristics of studied infants.

Clinical characteristics	*N* = 26
Gestational age (weeks)	32 (26–34)
Birth weight (g)	1635 (1350–1767)
Birth weight <10th percentile	3/26 (12)
Female	9/26 (35)
Cesarean delivery	20 (77)
Apgar score at 5 min	8 (8–9)
Antenatal steroids	19 (73)
Age at ultrasound study (h)	
Loading dose	3 (2–5)
Maintenance dose	26 (25–29)
Noninvasive respiratory supports	18/26 (69)
CPAP	15/26 (58)
NIPPV	3/26 (12)
Duration (h)	71 (53–90)
Surfactant therapy	4/26 (15)
Late onset sepsis (LOS)	1 (4)
Necrotizing enterocolitis (NEC)	1 (4)
Bronchopulmonary dysplasia (BPD)	1 (4)
Intraventricular hemorrhage (IVH)	1 (4)
Length of hospital stay (d)	33 (22–41)
Pregnancy pathologies	
Preeclampsia	3/26 (12)
Premature rupture of membranes	10/26 (38)
Clinical chorioamnionitis	2/26 (8)
Placental abruption	0/26

Note: Median and (interquartile range) or rate and (%).
Abbreviation: CPAP, continuous positive airway pressure.

TABLE 2 Comparison of diaphragmatic contractility ultrasound parameters detected before (T_0) and after (T_{60}) loading and maintenance dose of caffeine.

	Caffeine loading dose ($n = 26$)			Caffeine maintenance dose ($n = 26$)		
	T_0	T_{60}	p	T_0	T_{60}	p
DE (mm)	3.47 ± 1.24	4.50 ± 1.23	<0.001	3.77 ± 1.6	4.45 ± 1.51	<0.001
DT-in (mm)	1.42 ± 0.43	1.62 ± 0.48	0.003	1.27 ± 0.31	1.51 ± 0.45	<0.001
DT-ex (mm)	1.06 ± 0.29	1.24 ± 0.37	0.002	0.99 ± 0.29	1.15 ± 0.38	0.005
DTF (%)	32.7 ± 14.4	33.7 ± 14.7	0.606	30.6 ± 13.7	32.6 ± 12.1	0.578
I-Peak (cm/s)	1.31 ± 0.19	1.69 ± 0.39	<0.001	1.38 ± 0.25	1.73 ± 0.31	<0.001
E-Peak (cm/s)	1.30 ± 0.21	1.66 ± 0.35	<0.001	1.36 ± 0.23	1.62 ± 0.33	<0.001

Note: Mean ± SD.

Abbreviations: DE, diaphragmatic excursion; DT-ex, diaphragmatic thickness during expiration; DTF, diaphragmatic thickening fraction; DT-in, diaphragmatic thickness during inspiration; E-Peak, peak velocity of expiratory diaphragmatic excursion; I-Peak, peak velocity of inspiratory diaphragmatic excursion.

the M-mode technique with 10–12 MHz linear probe positioned perpendicular to the RD at the eighth or ninth intercostal space between the anterior axillary line and the middle axillary line. All measurements were obtained by calculating an average of at least five readings, recorded with the infant in a resting state with regular breathing. Diaphragmatic thickening fraction (DTF) was calculated using the following formula: DTF = ([DT-in − DT-ex]/DT-ex) × 100[20] (Supporting Information: Figure S1).

Measurements of the diaphragmatic excursion (DE) were performed using a 5 MHz sector probe positioned at the intersection of the right midclavicular line and right subcostal margin with the liver serving as a sound window, using the M-Mode technique. The position parallel to the diaphragmatic movement makes it possible to detect the extent of oscillation of the muscle toward and far from the probe which can be measured on the vertical axis (Supporting Information: Figure S2).

The peak velocity of excursion of the RD was studied using Pulse Wave Tissue Doppler Imaging (PW-TDI), both during inspiration (peak inspiratory velocity [I-Peak]) and expiration (peak expiratory velocity [E-Peak]). Measurements were performed as previously reported and the sample volume size for the PW-TDI analysis was set at 5 mm[19–21] (Supporting Information: Figure S3).

Ultrasound diaphragmatic evaluations were performed by M. F., M. C., V. L., and I. C. Preliminary measurements demonstrated low intra- and interobservers' variability (unreported data).

2.3 | Clinical data recording

Clinical and demographic data were collected by examining patients' medical records. The following data were recorded for each patient: gestational age, BW, BW <10th percentile, sex, mode of delivery, Apgar score at 5 min, antenatal steroids, age at the time of the study, type and duration of noninvasive respiratory support, need for surfactant, heart and respiratory rate, peripheral oxygen saturation (SpO_2), fraction of inspired oxygen (FiO_2), and SpO_2/FiO_2 ratio before and after caffeine administration, occurrence of sepsis, IVH, BPD, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and length of hospital stay. The diagnosis of sepsis was based on clinical and laboratory data (total neutrophil count, C-reactive protein, procalcitonin) confirmed by the presence of at least one positive blood or liquor culture. BPD was defined based on the classification of Jobe et al.[22] The adapted classification of Papile et al. was used to classify the severity of IVH.[23] The diagnosis of NEC was made according to Bell's criteria.[24] ROP was evaluated in accordance with the International Classification of ROP.[25] Moreover, we recorded main pregnancy pathologies, such as preeclampsia, premature rupture of membranes, clinical chorioamnionitis, and placental abruption.

2.4 | Statistical analysis

The sample size was calculated taking into account that the median contraction rate (TDI-PW I-Peak) of the RD in a population of infants born ≤34 weeks of gestational age is 1.30 (1.05–1.87).[25] Assuming that caffeine can induce an increase of 10% in TDI-PW I-Peak at T_{60}, we calculated a sample size of 20 infants to have a study with a statistical power of 80% at α 0.05.

Continuous variables were reported as mean and standard deviation, or median and interquartile range based on their distribution. Categorical variables were reported as rate and percentage. Normality distribution of data was assessed by the Kolmogorov–Smirnov test. Continuous variables were compared with Student's *t*-test or Mann–Whitney *U* test according to the normal distribution. Categorical variables were compared with Fisher's exact test. A $p < 0.05$ was considered statistically significant.

3 | RESULTS

We studied 26 preterm infants with median gestational age of 32 (26–34) weeks and BW of 1595 (1350–1767) g. Age of infants at diaphragmatic ultrasound was 3 (2–5) h of life for loading dose and 26 (25–29) h of life for maintenance dose. At the time of the study 18 (69%) infants required noninvasive respiratory support (Table 1).

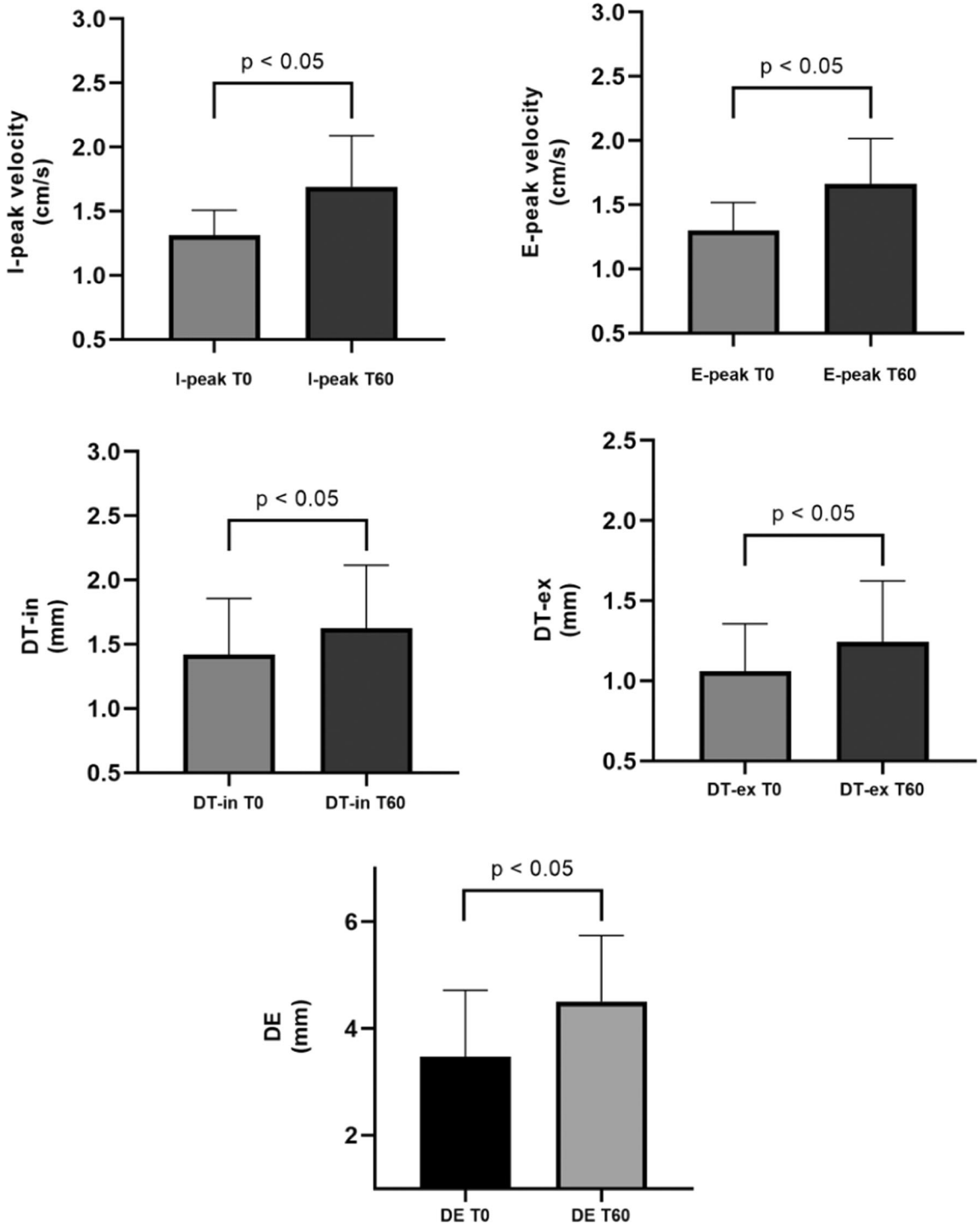

FIGURE 1 Peak inspiratory velocity of diaphragmatic excursion (I-Peak), peak expiratory velocity of diaphragmatic excursion (E-Peak), thickness of diaphragm during inspiration (DT-in), thickness of diaphragm during expiration (DT-ex), and diaphragm excursion (DE) measured 15 min before (T_0) and 60 min after (T_{60}) the administration of loading dose of caffeine.

The DE, DT-in, DT-ex values significantly increased after administration of both loading and maintenance dose of caffeine, while DTF did not vary (Table 2). Similarly, I-peak and E-peak of RD increased after caffeine treatment both after loading and maintenance dose (Table 2, Figures 1 and 2). Loading and maintenance dose of caffeine had similar effects on diaphragmatic I-peak, E-peak, DE, DT-in, DT-ex, and DTF (Table 2), as confirmed by the comparison of changes from T_0 to T_{60} of measured diaphragm contractility and motility parameters (Table 3).

We did not observe changes of heart and respiratory rate, SpO_2, FiO_2, and SpO_2/FiO_2 ratio after administration of loading and maintenance dose of caffeine (Supporting Information: Table S1).

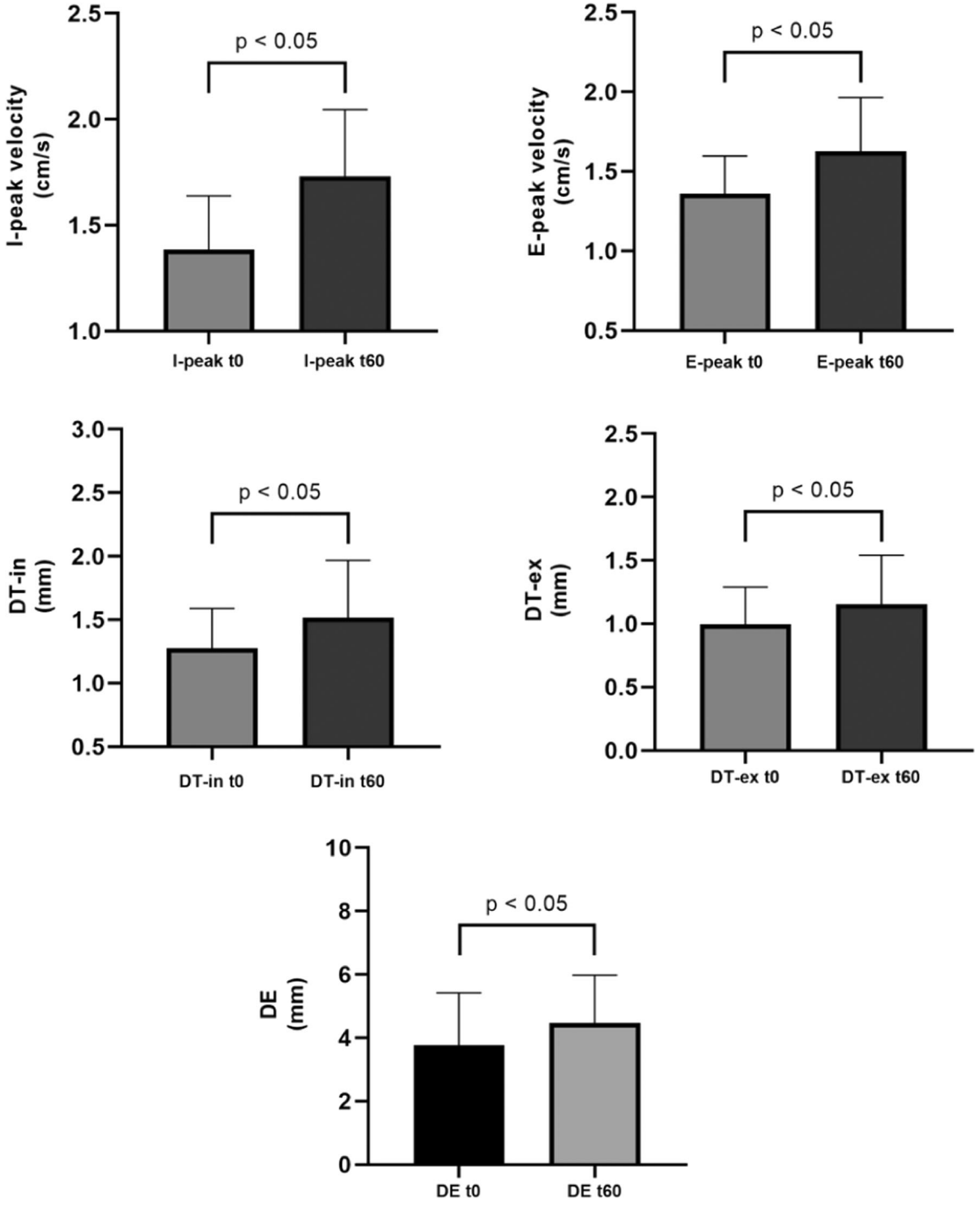

FIGURE 2 Peak inspiratory velocity of diaphragmatic excursion (I-Peak), peak expiratory velocity of diaphragmatic excursion (E-Peak), thickness of diaphragm during inspiration (DT-in), thickness of diaphragm during expiration (DT-ex), and diaphragm excursion (DE) measured 15 min before (T_0) and 60 min after (T_{60}) the administration of maintenance dose of caffeine.

4 | DISCUSSION

In this study we measured for the first time by ultrasound the effects of caffeine on the diaphragmatic activity in a cohort of preterm infants at risk or with AOP. We confirmed that caffeine increases the contractility and motility of the diaphragm both after loading and maintenance dose, as demonstrated by the observed increase in DE, DT-in, DT-ex, DTF, I-Peak, and E-Peak. These beneficial effects were observed, as expected, at the time of expected caffeine peak serum (T_{60}) which occurs 30–120 min after its administration.[12]

Our measurements of DE, DT-In, Dt-Ex, and DTF were in agreement with previous studies.[19,26,27] Bahgat et al. found that very preterm infants ($n = 43$) who were successfully extubated have greater expiratory diaphragm thickness and excursion as

TABLE 3 Comparison of changes from T_0 to T_{60} of diaphragmatic contractility ultrasound parameters associated with loading and maintenance dose of caffeine.

	Caffeine loading dose ($n = 26$)	Caffeine maintenance dose ($n = 26$)	p
I-peak (cm/s)	0.38 ± 0.35	0.34 ± 0.24	0.980
E-peak (cm/s)	0.36 ± 0.30	0.27 ± 0.20	0.134
DE (mm)	1.03 ± 0.93	0.68 ± 0.85	0.166
DT-in (mm)	0.20 ± 0.32	0.24 ± 0.27	0.891
DT-ex (mm)	0.18 ± 0.27	0.16 ± 0.26	0.508
DTF (%)	0.96 ± 9.37	2.00 ± 18	0.779

Note: Mean ± SD.

Abbreviations: DE, diaphragmatic excursion; DT-ex, diaphragmatic thickness during expiration; DTF, diaphragmatic thickening fraction; DT-in, diaphragmatic thickness during inspiration; E-Peak, peak velocity of expiratory diaphragmatic excursion; I-Peak, peak velocity of inspiratory diaphragmatic excursion.

assessed by ultrasounds than those for whom extubation was not successful.[19]

Alonso-Ojembarrena et al. reported references values of DT and shortening fraction in asymptomatic term ($n = 33$) and preterm ($n = 33$) infants and did not find differences between them.[26] Rehan et al. demonstrated that higher levels of continuous positive airway pressure (CPAP) are associated with an increased DT and decrease the amplitude of DE suggesting that an excessive CPAP level can induce contractility dysfunction.[27] Overall, these studies[19,27] suggest that in preterm infants DT and excursions are positively correlated with the strength of diaphragmatic contraction.[28] Thus, an increase of thickness can reflect a self-compensative mechanism which acts in the acute phase of RDS and is close to failing when thickness is high but amplitude of DE is low.[26] Conversely, high levels of both thickness and excursion amplitude predict an increased probability of successful extubation during the recovery phase of RDS.[19] Thus, the increase of DT and excursions that we found with diaphragmatic ultrasounds after caffeine treatment is consistent with the effectiveness of this drug in preventing extubation failure[5] by increasing the contractility strength of the diaphragm.

In our study, we assessed the peak velocity of inspiratory (I-Peak) and expiratory (E-Peak) DE using the PW-TDI ultrasound technique. This method seems to provide a more accurate evaluation of the diaphragmatic function allowing measurement of its contraction velocity during both inspiration and expiration.[28] Reference values of I-Peak and E-Peak were reported in healthy term infants excluding changes depending on the mode of delivery and sex.[28] Moreover, the possible correlation between I-Peak and E-Peak values and the risk of nasal CPAP failure was studied in preterm infants with RDS demonstrating that an increased E-Peak is correlated with an increased risk of nCPAP failure. This suggests that an increase of E-Peak can represent a protective compensation which counteracts the worsening of RDS and, simultaneously, warns against the risk of a possible failure of nCPAP. Thus, our observation that caffeine increases both I-Peak and E-Peak in preterm infants confirms that caffeine can contribute to limit the severity of respiratory failure and decrease the need and duration of mechanical ventilation[29,30] by enhancing the strength of diaphragmatic contraction and, on turn, the effectiveness of noninvasive ventilation.[30] In fact, it has been demonstrated in adults that the increase of velocity of DE promotes an increase of parameters of lung mechanics (i.e., forced vital capacity, maximum inspiratory pressure, maximum expiratory pressure) which reflect diaphragmatic strength.[31]

A limitation to our study was that some patients required noninvasive respiratory support while others did not, and that the former received a different type of respiratory support. However, all infants treated with noninvasive respiratory support had mild-to-moderate RDS, as confirmed by the fact that none of them required mechanical ventilation. Therefore, we are confident that our population was adequately homogeneous to support the accuracy and reproducibility of our data.

5 | CONCLUSION

This study demonstrates for the first time the beneficial effects of caffeine on diaphragmatic function using ultrasound techniques. We confirmed that caffeine improves the activity of the diaphragm demonstrating that after its administration there is an increase of thickness, amplitude of excursions, and contraction velocity. These improvements indicate that caffeine can increase the strength of diaphragmatic contractions and help explain its effectiveness in treating AOP and counteracting respiratory failure in preterm infants with RDS. Point-of-care ultrasonography is confirmed to be a useful tool for assessing respiratory function in NICU.

AUTHOR CONTRIBUTIONS

Carlo Dani: Conceptualization; methodology; formal analysis; supervision; writing—original draft; writing—review and editing. **Monica Fusco**: Investigation; data curation; methodology; writing—review and editing. **Sara Manti**: Methodology; investigation; writing—review and editing; data curation. **Lucia Marseglia**: Methodology; investigation; writing—review and editing; data curation. **Martina Ciarcià**: Methodology; investigation; writing—review and editing; data curation. **Valentina Leonardi**: Investigation; methodology; data curation; writing—review and editing. **Iuri Corsini**: Methodology; writing—review and editing; investigation; data curation. **Eloisa Gitto**: Conceptualization; methodology; writing—review and editing; validation. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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The authors have nothing to report.

CONFLICTS OF INTEREST STATEMENT

Prof. Carlo Dani received honoraria from Chiesi Farmaceutici SpA and Vyaire Medical Inc. for scientific consultancy. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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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