Diaphragm Dimensions of the Healthy Preterm Infant

Virender K. Rehan, MD*; JoAnn Laiprasert*; Michael Wallach, MD‡; Lewis P. Rubin, MD§; and F. Dennis McCool, MD||

ABSTRACT. Background. The diaphragm is the major inspiratory muscle in the neonate; however, human neonatal diaphragm development has not been extensively studied. We hypothesized that diaphragm thickness (tdi) would be positively related to postmenstrual age (PMA), body weight, body length, head circumference, and nutritional intake.

Objectives. To evaluate the evolution of diaphragm growth and motion in the healthy, preterm infant.

Methods. We used ultrasound to measure tdi at the zone of apposition to the rib cage and diaphragm excursion (edi) during inspiration. Thirty-four stable, preterm infants (16 males and 18 females) between 26 and 37 weeks’ PMA were studied during quiet sleep at weekly intervals until the time of discharge or transfer from the neonatal intensive care unit. All infants were clinically stable and not receiving ventilatory support.

Results. We found that 1) tdi increased from 1.2 ± 0.1 to 1.7 ± 0.05 mm between 26 to 28 and 35 to 37 weeks’ PMA; 2) tdi was positively correlated with PMA (r = 0.40), body weight (r = 0.52), body length (r = 0.53), and head circumference (0.49), but not with postnatal nutritional intake (r = 0.09); and 3) edi decreased with increasing PMA.

Conclusions. Our findings suggest that diaphragm development in premature infants scales with body dimensions. We speculate that the increase in tdi with age is likely attributable to increased diaphragm muscle mass, and the reduced edi with age may be resulting from a reduction in chest wall compliance. Pediatrics 2001; 108(5). URL: http://www.pediatrics.org/cgi/content/full/108/5/e91; diaphragm, development, ultrasound.

ABBREVIATIONS. tdi, diaphragm thickness; FRC, functional residual capacity; Δtdi, change in diaphragm thickness; PMA, postmenstrual age; BL, body length; HC, head circumference; NI, nutritional intake; GA, gestational age; e di, diaphragm dome excursion; BW, body weight.

The diaphragm is the major inspiratory muscle in the neonate; however, little is known regarding human postnatal diaphragm development. In animal studies, the diaphragm undergoes significant structural and functional changes during the postnatal period.1–9 There is hypertrophy of myofibers and changes in myofiber type and density that start during late gestation and continue for a variable period after birth.5,9,10 Similar changes may occur with the human diaphragm during this period of early growth. However, there is only limited information from autopsy and functional studies in infants and children, and there is no normative data for human neonatal diaphragm dimensions and how these dimensions change with growth.11–15 Such information may provide some insight as to why this population is at risk of developing respiratory failure.

The invasive nature of most methods used to assess diaphragm structure in animals limits their utility in humans. By contrast, ultrasound provides a noninvasive means of assessing the diaphragm in adults, children, and neonates.16–18 In adults, diaphragm thickness (tdi), measured at functional residual capacity (FRC), is proportional to diaphragm strength. tdi increases with inspiratory muscle training, and decreases with disuse.16,19–21 Furthermore, the change in tdi during inspiration (Δtdi) provides a measure of diaphragm shortening during inspiration in both adults and term infants.16,22 Thus, the noninvasive nature of diaphragm ultrasonography makes it amenable to the longitudinal study of the diaphragm as it is dynamically changing during early growth and development. The present study was designed to characterize the evolution of tdi in stable preterm infants during the early weeks of neonatal growth. Based on literature and our previous observations in adults and children, we hypothesized that tdi would be positively related to gestation and postmenstrual age (PMA), body length (BL), head circumference (HC), and nutritional intake (NI) in preterm infants.19,23–25

METHODS

Participants

We recruited 34 (16 males and 18 females) clinically stable, preterm infants between the gestational ages (GA) of 26 to 32 weeks (Table 1). Estimation of GA was based on the best obstetrical assessment and modified Ballard scoring.26 There was no evidence of any acute illness in the infants at the time of the study. Exclusion criteria included clinical instability, culture proven sepsis, current oxygen supplementation, continuous positive airway pressure or ventilatory support, congenital malformations, and grade II intraventricular hemorrhage. Written parental consent was obtained for each infant before the study. The Institutional Review Board of the Women and Infants’ Hospital of Rhode Island approved all studies.

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INTERPRETATION

We longitudinally measured \( t_{di} \) and \( e_{di} \) in 34 stable preterm infants, and described the relationship between \( t_{di} \) and PMA, BW, BL, HC, and NI. We found that \( t_{di} \) was positively associated with postmenstrual age. At 26 to 28 weeks’ PMA, the diaphragm was significantly thinner than at 35 to 37 weeks’ PMA. On average, \( t_{di} \) increased by 0.1 mm/week between 26 and 37 weeks’ PMA. We speculate that the progressive increase in \( t_{di} \) with increasing maturation results from a combination of an increase in the number of myofibers as well as to myofiber hypertrophy.

The increase in \( t_{di} \) with maturation most likely

### RESULTS

A total of 190 observations were recorded for each parameter (\( t_{di} \), \( \Delta t_{di} \), \( \%t_{di} \), \( e_{di} \), NI) in the 4 PMA categories: 22 between 26 and 28 weeks, 56 between 29 and 31 weeks, 70 between 32 and 34 weeks, and 42 between 35 and 37 weeks. Infants were grouped in PMA categories according to the completed week of PMA, eg, an infant at 28 3/7 weeks was placed into the 26 to 28 weeks’ PMA group and an infant at 34 2/7 into the 32 to 34 PMA group. The number of observations made for each infant ranged between 2 and 11 (median: 5). The coefficient of variation for measurements of \( t_{di} \) was 9.8%. This degree of reproducibility of \( t_{di} \) was similar to what we have previously reported in adults and infants.\(^ {17,22} \). Group mean values of \( t_{di} \), \( \Delta t_{di} \), \( \%t_{di} \), \( e_{di} \), and NI for each PMA category are shown in Table 2.

For pooled data, the relationship between \( t_{di} \) and PMA is shown in Fig 1 and among \( t_{di} \) and BW, BL, and HC in Fig 2. \( t_{di} \) progressively increased with increasing PMA (1.2 mm at 26–28 weeks vs 1.7 mm at 35–37 weeks; \( P < .05 \), \( r = 0.40 \)). The increase in \( t_{di} \) with maturation was proportional to the increase in BW, BL, and HC with growth (\( r = 0.52, 0.53, \) and 0.49, respectively). \( t_{di} \) scaled with BW to the mean power of 0.61 (\( t_{di} \sim BW^{0.61} \)). By contrast, there was no significant relationship between \( t_{di} \) and NI (Fig 3). Average daily caloric intake (NI) was higher at lower GAs.

The percent change in \( t_{di} \) during inspiration (\( \%\Delta t_{di} \)) (change in \( t_{di} \) relative to \( t_{di} \) at FRP = \( \Delta t_{di}/t_{di} \) (FRP) \( \times 100 \)) for each group is presented in Table 2. The \( \%\Delta t_{di} \) is proportional to the degree of diaphragm shortening during inspiration. As the diaphragm shortens, it is displaced caudally. This excursion of the diaphragm dome was measured as \( e_{di} \). With tidal breathing, the \( \%\Delta t_{di} \) was not significantly different for all PMA categories studied. (23% at 26–28 weeks vs 25% at 35–37 weeks’ PMA; \( P > .05 \)), but there was a significant decrease in \( e_{di} \) with increasing maturation (5.5 mm at 26–28 weeks vs 4.4 mm at 35–37 weeks’ PMA; \( P < .05 \), Fig 4).

### DISCUSSION

The infants were separated into 4 groups according to PMA; 26 to 28, 29 to 31, 32 to 34, and 35 to 37 weeks. Analysis of variance for repeated measures was used to assess differences in \( t_{di} \), \( \Delta t_{di} \), \( e_{di} \), and NI among different groups. If significant differences were found by analysis of variance, Newman-Keuls posthoc testing was used to detect differences among study periods. Linear regression and \( t \) tests were performed as appropriate. The influence of GA, various anthropometric parameters, and NI on \( t_{di} \) was assessed using mixed models regression to account for correlations within the participants.\(^ {26} \) A \( P \) value of < .05 was considered significant.

<table>
<thead>
<tr>
<th>TABLE 1. Patient Characteristics</th>
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<tr>
<td><strong>PMA (Weeks)</strong></td>
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<td><strong>Participants (n)</strong></td>
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<tr>
<td><strong>BW (g)</strong></td>
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<td><strong>BL (cm)</strong></td>
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<td><strong>HC (cm)</strong></td>
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<td>BW, BL, and HC values are means ± standard error of the mean.</td>
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### Measurements

The infants were studied while sleeping quietly in the supine position and at least 1 hour postprandial. The diaphragm was visualized using a 7.5-MHz transducer placed in right midaxillary line at the level of the zone of apposition of the diaphragm to the rib cage. Ample prewarmed ultrasound gel was used to maintain acoustic coupling and to ensure good image quality throughout the imaging process. Using the B-mode, 2-dimensional coronal images of the diaphragm were generated and selected for clarity and parallelism for the 3 layers of diaphragm structure: the pleural reflection, muscular layer, and the peritoneal reflection.\(^ {21} \) The infant’s breathing was recorded for 1 minute and replayed on the ultrasound screen to exactly time the beginning and end of each respiratory cycle. The freeze frame control allowed us to determine precisely end-inspiration and end-expiration (E). Diaphragm thickness was measured as the perpendicular distance between the pleural and peritoneal reflections. Values reported for \( t_{di} \) are those obtained at FRC. The change in \( t_{di} \) during inspiration (\( \Delta t_{di} \)) was measured as the difference in \( t_{di} \) between end-expiration and end-inspiration for each volume. For each measurement of \( t_{di} \) and \( \Delta t_{di} \) at least 5 breathing cycles were analyzed.

To assess diaphragm dome excursion (\( e_{di} \)) during inspiration, the diaphragm was visualized in the sagittal plane by placing the transducer under the right costal margin in the mid-clavicular line. Motion of the dome was observed in real time and recorded on videotape for later review and analysis. Diaphragm excursion during inspiration was measured as the maximum caudal descent of the midpoint of the posterior third of the diaphragm between end-expiration and end-inspiration. An average \( e_{di} \) for 5 consecutive quiet breaths was obtained. A single investigator performed all ultrasound scans (J.L.).

Heart rate, respiratory rate, and arterial oxygen saturation were monitored continuously during the measurements of diaphragm dimensions. Sleep state was characterized by behavioral criteria as active or quiet, and all studies were conducted during quiet sleep.\(^ {27} \) Body weight (BW), BL, and HC were measured using standard techniques. NI was assessed as daily kilocaloric intake. The enrolled infants were followed longitudinally and measurements of \( t_{di} \), \( \Delta t_{di} \), BW, BL, and HC were recorded once weekly until the infant was discharged or transferred out of the neonatal intensive care unit. To ensure that the same diaphragm segment was followed longitudinally, measurements of \( t_{di} \) were obtained at the same external chest wall locations (8th or 9th intercostal space in the right midaxillary line) for each infant at every recording. Furthermore, as in our previous study in term infants, we found that in preterm infants, \( t_{di} \) is uniform over the 2 to 3 intercostal spaces scanned.

### Analysis

The infants were separated into 4 groups according to PMA; 26 to 28, 29 to 31, 32 to 34, and 35 to 37 weeks. Analysis of variance for repeated measures was used to assess differences in \( t_{di} \), \( \Delta t_{di} \), \( e_{di} \), and NI among different groups. If significant differences were found by analysis of variance, Newman-Keuls posthoc testing was used to detect differences among study periods. Linear regression and \( t \) tests were performed as appropriate. The influence of GA, various anthropometric parameters, and NI on \( t_{di} \) was assessed using mixed models regression to account for correlations within the participants.\(^ {26} \) A \( P \) value of < .05 was considered significant.

Values are means ± standard error of the mean. * \( P < .05 \) versus 35 to 37 weeks’ PMA.

<table>
<thead>
<tr>
<th>TABLE 2. Diaphragm Dimensions and NI in Different PMA Categories</th>
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<tr>
<td><strong>PMA (Weeks)</strong></td>
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<td><strong>( t_{di} ) (mm)</strong></td>
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<td><strong>( \Delta t_{di} ) (mm)</strong></td>
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<td><strong>( e_{di} ) (mm)</strong></td>
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<tr>
<td><strong>NI (kcal/k/d)</strong></td>
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* Values are means ± standard error of the mean. * \( P < .05 \) versus 35 to 37 weeks’ PMA.
increases diaphragm strength. However, a number of factors may affect the relationship between \( t_{di} \) and diaphragm strength, especially in the growing infant. First, maximal transdiaphragmatic force depends on the maximal specific force of the diaphragm myofibers. The specific force of neonatal diaphragm is less than the adult. With maturation, there is greater expression of the adult myosin heavy chain phenotype. This would increase specific force and therefore maximal transdiaphragmatic force for a given muscle cross-sectional area.\(^{15}\) Second, with maturation the myofibers become more closely packed as the interstitial water compartment decreases.\(^{35}\) This also increases maximal transdiaphragmatic force for a given \( t_{di} \). Finally, changes in diaphragm configuration will affect the relationship between maximal transdiaphragmatic force and pressure. Devlieger's\(^{29}\) work suggests that there are important configurational changes of the diaphragm between birth and adulthood. However, in contrast to his assertion that the zone of apposition is minimal or even absent in the neonate, we had no difficulty in visualizing the zone of apposition in even the most premature infant studied. The presence of a zone of apposition would improve the coupling of the diaphragm to the rib cage.

The increase in \( t_{di} \) with growth was significantly related to BW and length. In our previous cross-sectional study of children and adults of different sizes, we found that \( t_{di} \) scaled with BW to the 0.52 power and with height to the 1.82 power.\(^{16}\) In the absence of specific adverse influences on diaphragm development such as prolonged ventilatory support, asymmetric intrauterine growth restriction, and neurologic deficits, we may expect similar relationships in the growing newborn. In our current study, \( t_{di} \) scaled with BW to the 0.61 power. This closely approximates our previous findings of the relationship between \( t_{di} \) and BW in term infants as \( t_{di} \sim BW^{0.57} \) and in older children and adults as \( t_{di} \sim BW^{0.52}.^{17,22} \) Our finding that \( t_{di} \) scales with BW is consistent with previous observations that diaphragm mass is proportional to body mass in the growing animal as well as in normal adult men of different BWs.\(^{23,36-39} \) and extends these observations to the healthy preterm infant. This proportionality between \( t_{di} \) and body size may account for the relative constancy of maximal transdiaphragmatic pressures among species of different sizes.\(^{40}\)

A number of studies suggest that preterm infants tolerate respiratory loads poorly and are at higher risk for respiratory failure when compared with older infants and children.\(^{5,30,31}\) This was thought to be because of the relative lack of highly oxidative, fatigue resistant type I fibers, in the neonatal diaphragm.\(^{11}\) In animal models and humans, diaphragm myofiber composition changes significantly during postnatal development.\(^{1,3,7,9,11,32-34}\) However, it is now clear that the overall oxidative capacity of the neonatal diaphragm cannot be reliably

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Fig 1. \( t_{di} \) is positively correlated (\( r = 0.40 \)) with PMA.

Fig 2. \( t_{di} \) is positively correlated with BW (\( r = 0.52 \)), BL (\( r = 0.53 \)), and HC (0.49).
predicted from the relative proportions of type I and type II fibers present histochemically. Animal studies have consistently shown that, studied in vitro, neonatal diaphragm is more fatigue resistant compared with that of the adult. The myosin heavy chain phenotype during development alone seems to exert a strong predictive effect on fatigue resistance property of the diaphragm. This is primarily attributable to the low energy demands of the developmental myosin heavy chain isoforms present in the neonatal diaphragm. Indeed, limited human data on myosin heavy chain phenotype expression also suggests that neonatal diaphragm to be more fatigue resistant than its adult counterpart. Therefore, it is unlikely that the preterm infant’s inability to tolerate respiratory loads is because of its diaphragm fatigue, but may be attributable to a reduction in its specific force, its reduced thickness relative to later GAs, a decreased neuromuscular activation, or overall immature respiratory mechanics and other factors.

The time course of diaphragm development of the premature infant is thought to differ from that of the full-term infant. In prematurely delivered baboons, the diaphragm fibers are considerably smaller at equivalent PMAs when compared with baboons completing intrauterine development. This growth arrest of the diaphragm persists for at least 10 days after the premature delivery in the baboon model. By contrast, our healthy preterm infants increased \( t_{di} \) by 0.1 mm/week from birth onwards such that at 37 weeks’ PMA, \( t_{di} \) was similar to what we have previously reported for healthy term infants \( (t_{di} = 2.02 \text{ mm for preterm and } 1.97 \text{ mm for term infants}) \). Thus, the ex utero increase in \( t_{di} \) for stable preterm infants is similar to the in utero increase in \( t_{di} \) that occurs spontaneously during pregnancy. These contrasting results between the human and baboon diaphragm development either may reflect species differences or better overall care of the human premature infant in an intensive care setting. The impact of illness severity and greater respiratory and metabolic demands in sick preterm infants on extrauterine diaphragm development and function remains to be investigated.

The caudal motion of the dome of the diaphragm during tidal breathing \( (e_{di}) \) was greater in the most premature infants \( (5.5 \text{ mm at } 26–28 \text{ weeks vs } 4.4 \text{ mm at } 35–37 \text{ weeks’ PMA}) \). In adults, diaphragm activation during tidal breathing results in caudal descent of the diaphragm accompanied by expansion of the lower rib cage. In neonates, however, the lower rib cage often moves paradoxically inwards as the diaphragm descends during inspiration. Thus, for a given degree of diaphragm shortening, there is greater caudal motion of the diaphragm. With growth, there is a reduction in chest wall compliance and less lower rib cage distortion. The decrease in \( e_{di} \) with growth then may reflect more effective coupling of the diaphragm to the chest wall that results in less caudal descent for a given amount of diaphragm shortening. We speculate that the reduction in \( e_{di} \) with PMA, then, may be attributable to decreased chest wall compliance with maturation of the infant. Our finding that change in \( t_{di} \) during inspiration \( (%\Delta t_{di}) \) was unchanged with maturation supports this notion. If no accessory muscles are used in addition to the diaphragm, the %\( \Delta t_{di} \) is proportional to tidal volume. Although tidal volume was not measured directly in our study, the %\( \Delta t_{di} \) was unchanged; 23% at 26 to 28 weeks and 25% at 35 to 37 weeks’ PMA, respectively. Our observation that an increased \( e_{di} \) at lower PMAs occurs without a corresponding increase in %\( \Delta t_{di} \) is consistent with the notion that the diaphragm is more effectively coupled to the lower chest wall in more mature infants. In the premature infant, the diaphragm has to contract more to compensate for the tidal volume lost because of chest wall distortion.

The effects of nutritional deprivation on diaphragm structure and function are age and gender specific. Acute nutritional deprivation (90 hours) has no effect on rat diaphragm contractility or morphology and only an inconsequential influence on diaphragm fatigue; whereas prolonged undernutrition can result in deleterious changes in diaphragm muscle structure and impair its ability to generate force despite preserving its mechanical efficiency. We did not find a significant relationship between postnatal NI and \( t_{di} \). However, our study was not designed to test specifically the effects of postnatal undernutrition on diaphragm development. In the present study, most of these infants received paren-
teral nutrition early in their clinical course. This may account for the greater daily caloric intake/kg of BW at lower PMA. At later PMAs, caloric intake was provided solely by the enteral route. Reassuringly, the caloric intakes in these infants was sufficient to allow the diaphragm to grow to a similar thickness ex utero as compared with the $t_{di}$ observed in infants born at term.21

CONCLUSION

By using ultrasonography, we have established normative data for $t_{di}$ and excursion in healthy preterm infants. With increasing maturation, $t_{di}$ progressively increases and diaphragm excursion decreases. The significant correlations between $t_{di}$ and BW, BL, and HC extend the principles of scaling to premature infants. Ultrasonographic evaluation of diaphragm in premature infants, as described by us, may provide a noninvasive test for assessment of diaphragm development and function under different pathologic situations.

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