ORIGINAL ARTICLES

Expired Tidal Volume and Respiratory Rate During Postnatal Stabilization of Newborn Infants Born at Term via Cesarean Delivery

Susana Baixauli-Alacreu, CM[1,3,4], Celia Padilla-Sánchez, CM[1,3,4], David Hervás-Marín, MSc[2], Inmaculada Lara-Cantón, MD[1,5], Alvaro Solaz-García, RN[1,3], Maria José Alemany-Anchel, PhD[3,4], and Maximo Vento, MD, PhD[1,5]

Objective To retrieve evolving respiratory measures in the first minutes after birth in normal neonates born at term using a respiratory function monitor.

Study design We evaluated newborn babies delivered at term via cesarean after uncomplicated pregnancies. Immediately after birth, a respiratory function monitor with an adapted flowmeter and a face mask were applied at 2, 5, and 10 minutes after birth for 90 seconds in each period. We analyzed expired and inspired tidal volume, respiratory rate (RR), percentage of leakage, and number of analyzed breaths in each individual infant's recording using a respiratory research software.

Results A total of 243 infants completed the study. The final data set included 59 058 (48.35%) valid observations for each of the variables representing the analysis of 32 801 breaths. With these data, we constructed a reference range with 10th, 25th, 50th, 75th, and 90th percentiles for expired tidal volume and RR. Tidal volumes plateaued earlier in female than in male infants. No correlation with delayed cord clamping, gestational age, maternal morbidity, or indication for cesarean delivery were established.

Conclusions We have constructed a reference range with percentiles for inspired and expired tidal volumes and RR in newborn babies born at term for the first 10 minutes after birth. Reference ranges can be employed for research and can be useful in the clinical setting to guide positive pressure ventilation in the delivery room. *(J Pediatr: X 2021;6:100063)*.

Approximately 130 million babies are born every year worldwide, of whom 5%-10% will require respiratory support in the immediate postnatal period.[1,2] Cesarean delivery requires surgical intervention that increases the risk and severity of neonatal respiratory morbidity.[3,4] The cesarean delivery rate, even in high-income countries, exceeds the World Health Organization recommendations.[5,6] Consequently, postnatal care of babies born by cesarean delivery constitutes an important concern for neonatologist.[3,4]

Adequate lung ventilation is key to successful postnatal stabilization.[2,7,8] In newly born infants who do not initiate effective breathing despite tactile stimulation, positive pressure ventilation (PPV) should be rapidly provided.[9] The goal of PPV is to create a functional residual capacity (FRC), deliver an adequate tidal volume (V_T), normalize blood gases, and stimulate breathing while minimizing lung injury.[10] Optimal PPV should be guided by continuous monitoring of inspiratory and expiratory airway pressure, gas flow, V_T, and mask leakage[9,11]; these goals can be facilitated using a respiratory function monitor (RFM) during PPV in the delivery room (DR).[10,12]

Effective ventilation requires the provision of peak inspiratory pressure (PIP) capable of generating sufficient V_T to aerate the lungs and positive end-expiratory pressure that helps establish FRC sufficient to prevent alveolar collapse/atelectasis during expiration.[2,13] To achieve these ventilatory goals, V_T monitoring during PPV in the DR is more relevant than PIP.[10,13,14] Kattwinkel et al demonstrated that monitoring V_T better detected changes of lung compliance than monitoring pressure.[14] Hernandez et al concluded that pulmonary overdistension due to high V_T rather than high PIP caused lung damage.[15] Thus, to minimize volutrauma, PIP should be adjusted to ensure the delivery of a V_T within a safe range.[13] Schmölzer et al showed that setting a PIP of 30 cm H_2O could deliver V_T that ranged from 0 to 30 mL/kg.[12] Moreover, studies in animals revealed that V_T between 8 and

bpm	Breaths per minute	RFM	Respiratory function monitor
DCC	Delayed cord clamping	RR	Respiratory rate
DR	Delivery room	SpO_2	Oxygen saturation
FRC	Functional residual capacity	V_T	Tidal volume
PIP	Peak inspiratory pressure	V_{Te}	Expired tidal volume
PPV	Positive pressure ventilation	V_{Ti}	Inspired tidal volume

From the [1]Neonatal Research Group and [2]Data Science Unit, Health Research Institute La Fe; [3]Nursing School, University of Valencia; [4]Midwifery Teaching Unit, Generalitat Valenciana, Consellería de Salud; and [5]Division of Neonatology, University and Polytechnic Hospital La Fe, Valencia, Spain

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15 mL/kg[16,17] caused lung damage independent of PIP, suggesting that PIP varies according to the lung compliance.[16]

However, keeping the V_T within an established range using a pre-established PIP limit is difficult. Even in expert hands, airway obstruction and/or mask leakage are extremely common.[9] In addition, breathing efforts of the newborn infant will increase the inconsistency of volumes delivered with a fixed PIP.[9,13] However, if V_T is kept constant despite pressure changes, lung injury is likely to be minimized while ventilation remains adequate.[9,14] Thus, measuring and adjusting V_T during PPV may be particularly helpful during postnatal stabilization.[10,12,18,19] Previous studies on spontaneous breathing in newborns born at term suggest that the normal V_T ranges between 5 and 7 mL/kg.[20,21] However, these studies include limitations such as sample size or do not incorporate recent changes in the DR management such as delayed cord clamping (DCC) in babies born by cesarean delivery.[7]

We aimed to assess the normal V_T and respiratory rate (RR) in babies born at term via cesarean delivery in the first minutes after birth. We employed an RFM to retrieve changes in the expired tidal volume (V_{Te}) and RR in the first 10 minutes of life in healthy infants born at term via elective cesarean delivery, spontaneously breathing, without respiratory distress, and not needing resuscitation. Thus, we were able to define a reference range and construct a percentile graph to guide PPV but also positive end-expiratory pressure/continuous positive airway pressure level in spontaneously breathing infants during postnatal stabilization in the DR.

Methods

We conducted a prospective, single-center observational study of newborn infants born in the Obstetric Area of the University and Polytechnic Hospital La Fe (Valencia, Spain). Eligible Infants were born at ≥37 weeks of gestational age by elective cesarean delivery under spinal anesthesia and did not need ventilation or oxygen during DR stabilization. The current guidelines of the Spanish Neonatal Society indicate that babies born after elective cesarean delivery should be observed over a period of 10 minutes in the resuscitator. Conversely, babies born by vaginal delivery should be placed immediately on their mother's chest in a prone position for skin-to-skin contact.[22] Under these circumstances, the hospital ethics committee did not allow the use of RFM, which might interfere with maternal–infant bonding in vaginal deliveries. Thus, we excluded babies born by vaginal delivery, preterm, with congenital cardiac and respiratory malformations, or needing any type of intervention in the DR.

The study design was approved by the Ethics Committee of the University and Polytechnic Hospital La Fe, and informed consent was signed by parents of all the enrolled patients before birth.

Lung function and gas flow were assessed using a noninvasive RFM New Life Box Neo-RSD (Advanced Life Diagnostics UG) and New Life Box-R (Advanced Life Diagnostics UG), respectively.[23] An open 50-mm face mask (Fisher Paykel Healthcare) was placed upon the baby's face with the distal end open to the air, thus allowing the infant to breathe with minimal resistance.[24,25] The RFM uses a variable orifice anemometer (Avea Varflex Flow Transducer; CareFusion) to measure circuit pressure and gas flow in and out of a T-piece (**Figure 1**, A).

The dead space of the pneumotachograph is <0.7 mL[25,26] and of the mask approximately 20 mL[27]; providing a good seal significantly (**Figure 1**, B) reduced the mask dead space by 30%-40%.[28] The mask was applied at 2, 5, and 10 minutes after birth. Respiratory function was recorded for periods of 90 seconds in each period to avoid interfering with postnatal adaptation.[25]

The New Life Box Neo-RSD monitor exhibits graphical and numerical flow and volume information. All signals were digitized and recorded at 200 Hz using the Polybench neonatal physiological recording program (Applied Biosignals GmbH, edition 1.30.0.3505).[23]

In January 2019, the hospital guidelines started to recommend delaying cord clamping for 60 seconds, during which time the baby was dried and wrapped in warm clothes while the attending neonatologist supervised postnatal adaptation.[2,8] Tactile stimulation was only performed if babies did not initiate spontaneous breathing efforts 30 seconds after birth. If the transition was adequate, the face mask was applied at 2, 5, and 10 minutes after birth for 90 seconds. For this purpose, the baby was placed in a supine position and the head in a neutral position to keep the airway open.[8] The mask completely covered the nose and mouth area; the newborn's chin was held firmly in place to prevent leakage[25] (**Figure 1**, B). After 12 minutes, researchers stopped monitoring the infant. If there were signs of respiratory compromise, recruitment was suspended and ventilatory support was given according to neonatal resuscitation guidelines.[2,8] Researchers collecting respiratory data were independent of the attending clinicians and did not interfere with their decisions. A standardized protocol for the procedure and RFM data collection was established and measurements were performed by trained members of the research team.

A breath-by-breath analysis of each infant's recording was performed employing a data analysis software for respiratory research (Pulmochart; Advance Life Diagnostics).[29] This allowed for reproduction of the waveforms and breaths of each infant and eliminated possible noise and sensor interferences. Breath-by-breath analysis and breath elimination conditions are described in (**Table I**).[25,30–32]

We only included data recordings if there was a clean flow and V_T signal. For this purpose, we averaged the V_{Te} of 6 breaths in a row and satisfied the requirements as shown in **Table I**.[33] We retrieved the following respiratory parameters: V_{Te}, inspired tidal volume (V_{Ti}), RR, number

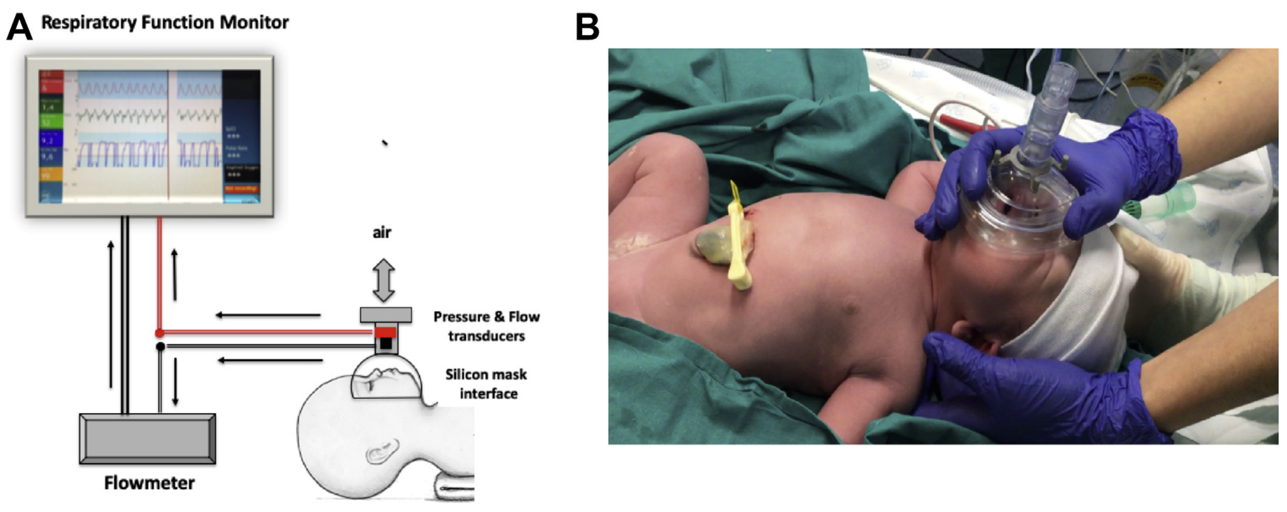

Figure 1. **A,** Scheme of the monitoring system. Face mask was applied to the infant's face covering nose and mouth. Sensors for monitoring respiratory parameters and flow were connected to the mask interface. Mask is open to air with neglectable expiratory resistance. **B,** Photograph depicting newborn's position and optimal mask holding during monitoring.

of analyzed breaths of each infant, and average percentage of leakage.

Statistical Analyses

Data were summarized using mean (SD) and median (first, third quartile) for continuous variables and relative and absolute frequencies for categorical variables. Bayesian spline percentile regression models were used to estimate the reference value curves of the parameters V_{Te} and RR. For each parameter the 50th, 25th, 75th, 10th, and 90th percentiles were estimated over the first 12 minutes of life. Because the study design was of repeated measurements, a random intercept was added for everyone to consider the dependence relationship of the observations of the same individual. As the use of splines makes the interpretation of the models difficult, nomograms were generated to facilitate the practical consultation of the reference values estimated by the different models.[34,35]

The leakage estimation through the mask is not possible when using an open system because there is no pressure inside the mask. Thus, the most reliable method to detect leakage was to calculate V_{Ti} and V_{Te} separately, omitting the use of automatic current correction algorithms, and comparing these values directly. The leakage was calculated as the percentage of gas volume that did not return through the flow sensor during expiration using the following formula: percentage of leakage = V_{Ti}–V_{Te}/V_{Ti} × 100.[36]

In addition, we studied the possible association of V_{Te} values with sex, DCC, indication for cesarean delivery, maternal morbidity, and gestational age. For this purpose, we averaged V_{Te} in the 30-second period that included the most representative values for each individual. The association between V_{Te} and each factor was analyzed using the Wilcoxon test for dichotomous factors and Kruskal–Wallis test in the case of factors with more than 2 categories. *P* values <.05 were statistically significant. Credibility or 95% CIs was obtained for all estimates. All analyses were performed using the software R (version 4.0; The R Foundation for Statistical Computing) and the packages click R (version 0.4.47; The R Foundation for Statistical Computing), brms (version 2.12), and splines (version 4.0).

Table I. Description of the circumstances that interfered with the assessment of physiologic breaths in the respiratory registries

Variables	Description
Flow and V_{Te}	Airway obstruction[25] coinciding with • Secretions • Neck hyperextension or flexion • Excessive pressure on the mask • Infant's movements • Mask leakage (abnormal positioning) • Sensor interfering with crying Panting pattern characterized by • Shallow breaths with VTs below the values established for anatomical dead space[25,30,31] Excessive V_T • V_T > total lung capacity referred to as 48 (IQR 43-52) mL/kg[32]
RR	Reliable range between 15 and 150 bpm[25]

Results

Between January 2018 and August 2019, a total of 243 infants completed the study. The final data set included 59 058 (48.35%) valid observations for each of the variables, which represented the analysis of 32 801 breaths (**Figure 2**). The characteristics of the infants and mothers are described in **Table II**.

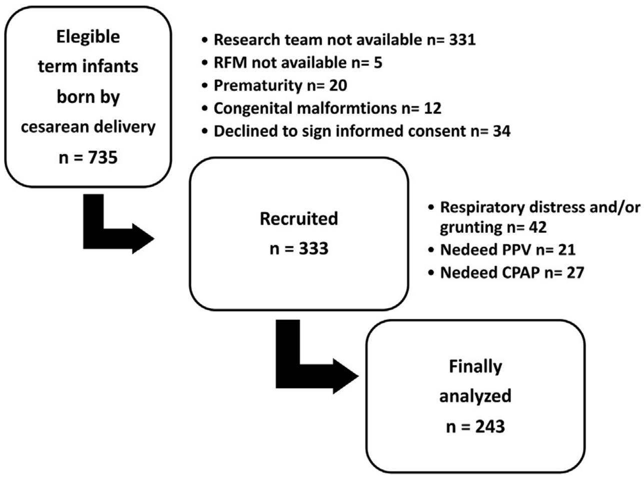

Figure 2. Flow diagram describing the recruitment process during the study. *CPAP*, continuous positive airway pressure.

We determined 10th, 25th, 50th, 75th, and 90th percentiles for V_{Te} and RR. Results are graphically depicted in **Figure 3**, A and B. Numerical values represented as a nomogram throughout the first 12 minutes of life are shown in **Figures 4** and **5**.

The Bayesian percentile regression models approach showed an upward trajectory for V_{Te} during the first 5 minutes of life that plateaued thereafter. For the 10th and 25th percentiles the trajectory remained constant throughout the period analyzed. The trajectory of the RR curves showed a similar tendency. The RR increased slightly until the sixth minute after birth and then plateaued.

Median and IQR of V_{Te} at 2, 5, and 10 minutes after birth were 4.2 (1.9-6.5), 4.9 (1.9-7.3), and 4.6 (1.9-6.6) mL/kg, respectively. Median (IQR) of RR at 2, 5, and 10 minutes after birth were 69 (53-82), 76 (60-90), and 78 (61-92), beats per minute (bpm), respectively.

Both V_{Te} and RR showed great variability throughout the first 12 minutes of life, ranging from 0.5 to 9.4 mL/kg for V_{Te} and 33 to 105 bpm for RR. We also analyzed the influence of different factors upon V_{Te}. Female infants obtained greater values of V_{Te} than male infants (P = .022, P = .002, and P = .008, at 2, 5, and 10 minutes after birth, respectively). No statistically significant association was found for DCC, maternal morbidity, gestational age, or indication for cesarean delivery. We also calculated the correlation between evolving V_{Te} with RR and oxygen saturation (SpO_2) in the first 12 minutes after birth; both V_{Te}/SpO_2 (ρ = 0.96) and V_{Te}/RR (ρ = 0.83) were significant.

Table II. Characteristics of mothers and infants included the study

Characteristics	Values N = 243
Mother's age, y (IQR)	36 (32, 39)
Maternal morbidities, no. (%)	52 (21.4%)
Elective cesarean delivery, no. (%)	222 (91.7%)
Failed induction/stopped birth, no. (%)	21 (8.2%)
Prenatal corticosteroids, no. (%)	13 (4.6%)
Gestational ages, wk, median (IQR)	39 (38.2, 39.2)
Birth weight, g, mean (SD)	3267 (571.85)
Female sex, no. (%)	125 (51.4%)
Apgar score at 1 min, median (IQR)	9 (9, 10)
Apgar score at 5 min, median (IQR)	10 (10, 10)
DCC (>30 s), no. (%)	62 (25.51%)
Time of DCC, s, mean (SD)	59.2 (12.14)

Discussion

We assessed evolving values for V_{Te} and RR in the first 10 minutes after birth in healthy infants born full term via elective cesarean delivery. Current evidence recommends that optimal ventilation should be guided by continuous visualization of airway pressure, gas flow, V_T, and mask leak.[9,11] Our data using a validated RFM provide reference ranges for V_{Te} and RR presented as a percentile chart, which could serve as guide for clinicians when applying PPV in the DR.

We observed that percentile curves for both V_{Te} and RR showed an increasing tendency immediately after birth (**Figure 3**, A and B) and plateaued at 5 and 6 minutes after birth, respectively. Of note, there was a highly significant correlation between V_{Te} and RR (ρ = 0.83) in the first minutes after birth. The interpretation of V_{Te} plateauing before RR may be because adequate V_{Te} favors the establishment of FRC, which in turn enhances alveolar–capillary gas exchange and subsequently reduces the RR. Moreover, SpO_2 in the first minutes after birth also significantly correlated with V_{Te} progression (ρ = 0.96). Our results coincide with data reported in other studies both in newborns born at term[20,21] and preterm.[37] Blank et al described a plateau of 5.3 mL/kg (2.5-8.4 mL/kg) at 130 seconds after birth.[21] In our study, we reached a plateau of 4.9 mL/kg (1.9-7.3) at 5 minutes of life. Notably, the study by Blank et al included both babies born by cesarean and vaginal delivery.[21] Babies born by vaginal delivery attain a V_{Te} plateau earlier than those born by cesarean delivery. Finn et al also showed a delay of V_{Te} stabilization between 3 and 4 minutes after birth in babies born by cesarean delivery.[20] This delay may be related with a slower extrusion of lung fluid to the interstitial space, or to an increased re-entry of lung fluid into the alveoli in the expiratory phase, thus hindering/delaying the establishment of an FRC.[38,39]

We established a median (IQR) for V_{Te} of 4.2 (1.9-6.5), 4.9 (1.9-7.3), and 4.6 (1.9-6.6) mL/kg at 2, 5, and 10 minutes after birth, respectively. Both Blank et al and Finn et al reported V_{Te} values similar to ours in the first minutes after birth.[20,21] Blank et al reported a V_{Te} of 5.3 mL/kg (2.5-8.4) and didn't find differences in V_{Te} between babies born by cesarean and vaginal delivery.[21] Finn et al registered a mean V_{Te} at 2 and 5 minutes of 5.7 (2.2) and 6.05 (2.4) mL/kg.[20] However, Schmölzer et al retrieved a mean V_{Te} of 6.3 ($\pm$3) mL/kg at

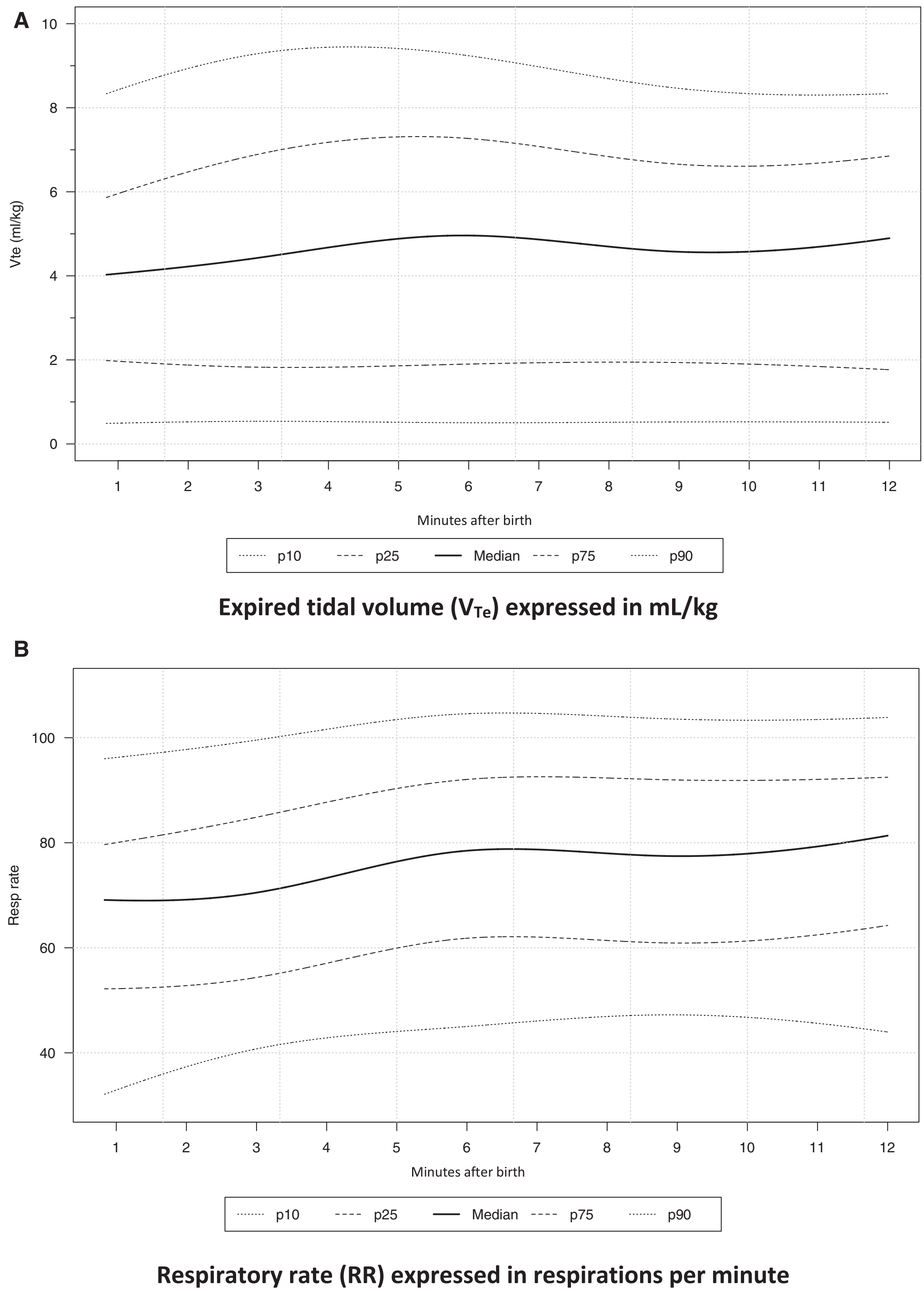

Figure 3. **A,** The 10th, 25th, 50th, 75th, and 90th percentiles of V_{Te} mL/Kg measured with an RFM in healthy newborns born at term via cesarean delivery and spontaneously breathing during the first 12 minutes after birth. **B,** The 10th, 25th, 50th, 75th, and 90th percentiles of RR bpm measured with an RFM in spontaneously breathing healthy term newborn infants born by cesarean delivery during the first 12 minutes after birth.

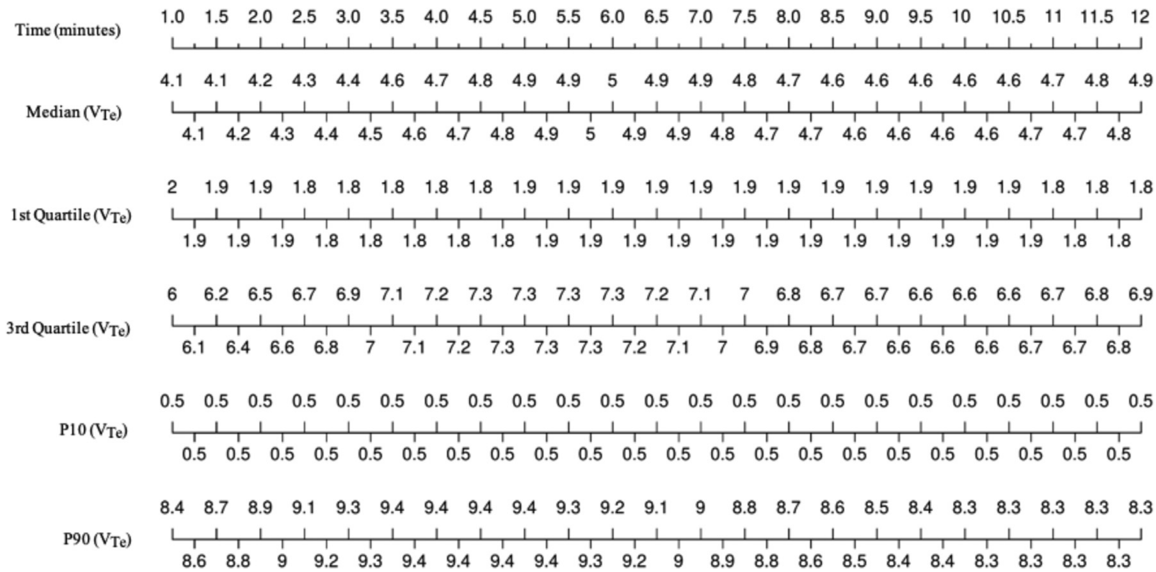

Figure 4. Percentiles of VTe mL/kg during the first 12 minutes of life in healthy infants born full term via elective caesarean delivery, with spontaneous breathing.

2 minutes of age, which is substantially greater than ours.[40] These differences in V_{Te} may be due to the smaller sample size in the study by Schmölzer et al and/or to the fact that V_{Te} was expressed as a mean, which is not as descriptive as the median.[40] Consistent with these reports, we observed a V_{Te} ranging between 4 and 6 mL/kg during the first minutes of life, indicating that babies born by cesarean delivery achieve similar V_T to those of babies born by vaginal delivery.[21,38]

Previous studies also reported a great variability of V_{Te}[21,37,41]; in our patients, V_{Te} ranged from 0.5 to 9.4 mL/Kg (10th and 90th percentile predictions). Variability could be attributed to reflex movements of the lower pharynx, epiglottis, and glottis.[41] These physiological adjustments are common during postnatal adaptation and are meant to provoke a positive end-expiratory pressure that contributes to the establishment of an FRC.[25] It should be noted that mask leakage in our study fluctuated between 16% and

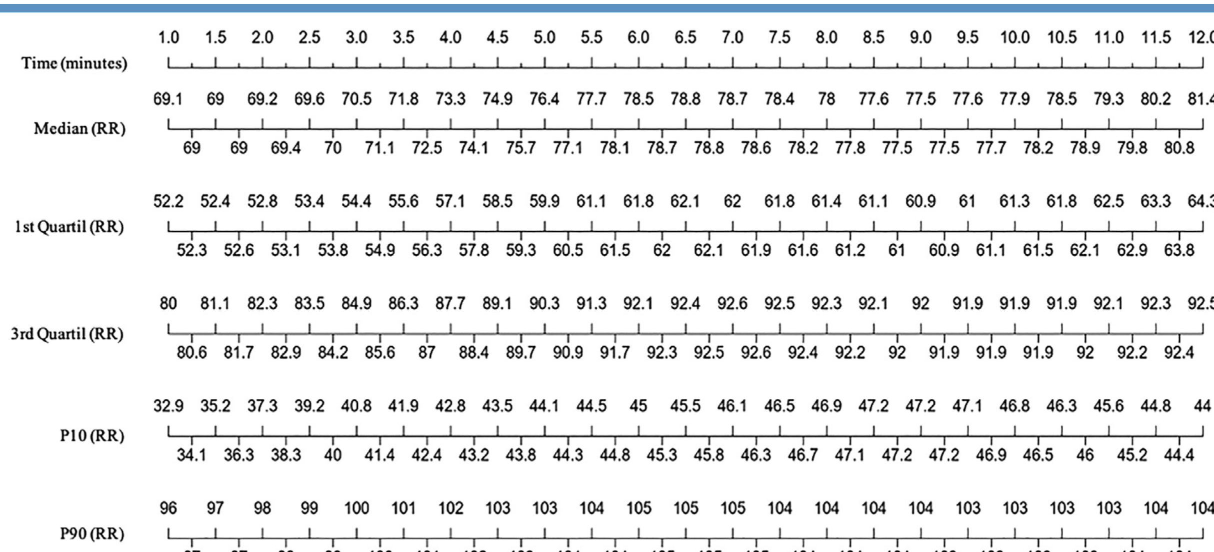

Figure 5. Percentiles of RR bpm during the first 12 minutes of life in healthy infants born full term via elective caesarean delivery, with spontaneous breathing.

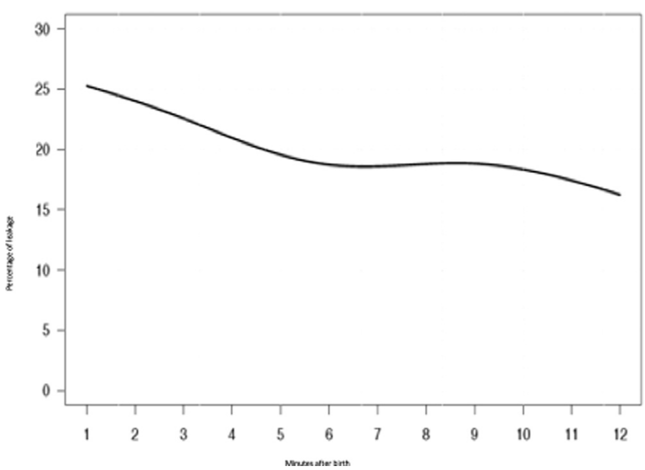

Figure 6. The graph shows the percentage of leakage (%) during the first 10 minutes after birth in heathy newborn babies born at term via cesarean delivery during the first 10 minutes after birth.

25% (**Figure 6**), which confirms that the V_{Te} depicted in the nomogram was a good estimate of the volume that entered the lungs.[42,43]

We also analyzed evolving RR. We reported a median and IQR of 69 (53-82), 76 (60-90), and 78 (61-92) bpm at 2, 5, and 10 minutes after birth. te Pas et al showed that babies during in the first minutes after birth presented a panting pattern with an average frequency of RR between 50 and 90 bpm.[25] We confirmed an increased incidence of transient tachypnea in our babies born by cesarean delivery, as has been previously described.[44] Although some previous studies found no difference in RR comparing mode of delivery,[21,38] perhaps our large sample size made the tachypnea more evident.

V_{Te} was influenced by the sex of the newborn infant: male newborn infants had significantly lower V_{Te} than girls at the same postnatal timings. Clinical studies on respiratory morbidity in infants born at term via cesarean delivery report that male sex has an increased the probability of admission to neonatal intensive care unit and/or suffering from respiratory distress syndrome.[44,45] We speculate this reflects a delay in lung maturation in male fetuses as compared with female fetuses.[46]

We acknowledge certain limitations to our study. The ethics committee didn't allow us to include babies born by vaginal delivery to avoid interfering with maternal–infant bonding and initiation of early breastfeeding. In addition, measuring respiratory changes with the RFM during the stabilization period in DR was technically very challenging.[21,25,47] To minimize interference with breathing, the mask was applied only for short periods of 90 seconds, which reduced the data available for analysis. In addition, all recordings with artifacts were excluded, which could lead to bias. We could not capture the first breaths, so it is possible that some early changes in V_{Te} and RR were not included.[41] In a recent study, it has been shown that the energic application of the face mask upon the face can stimulate the trigeminal nucleus and subsequently a vagal reflex, which can interfere the breathing pattern.[48] Notwithstanding, our results coincide with established ranges of V_{Te} described in previous studies.[9,13,20,21] Strengths of our study include a dedicated and trained team exclusively devoted to precisely make the measurements in the DR, the large number of analyzed registers, and the large sample size.

In conclusion, we present a reference range nomogram for V_{Te} and RR during the immediate postnatal adaptation of healthy infants born full term via cesarean delivery. The nomogram may be used to guide PPV when its directed by volume rather than pressure. Moreover, we found infants born by cesarean delivery required a longer period to reach a stable V_{Te} and RR than babies born by vaginal delivery, as deduced from published literature. We plan to enhance our studies by including infants born preterm. ■

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Reprint requests: Professor Máximo Vento, MD, PhD, Division of Neonatology, University and Polytechnic Hospital La Fe, Avenida Fernando Abril Martorell 106, 46026 Valencia, Spain. E-mail: maximo.vento@uv.es

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