# The Effect of Caffeine on Diaphragmatic Activity and Tidal Volume in Preterm Infants

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**Objective** To determine the effect of caffeine on diaphragmatic activity, tidal volume ($V_t$), and end-expiratory lung volume (EELV) in preterm infants.

**Study design** Using transcutaneous electromyography of the diaphragm (dEMG), we measured diaphragmatic activity from 30 minutes before (baseline) to 3 hours after administration of an intravenous caffeine-base loading dose in 30 spontaneously breathing preterm infants (mean gestational age, 29.1 ± 1.3 weeks), most of whom were on noninvasive respiratory support. Diaphragmatic activity was expressed as the percentage change in dEMG amplitude, area under the curve, respiratory rate, and inspiratory and expiratory times. Using respiratory inductive plethysmography, we measured changes in $V_t$ and EELV from baseline. These outcome variables were calculated at 8 fixed time points after caffeine administration (5, 15, 30, 60, 90, 120, 150, and 180 minutes) and compared with baseline.

**Results** Caffeine administration resulted in rapid (within 5 minutes) increases in dEMG amplitude (median, 43%; IQR, 24%-63%; $P < .001$) and area under the curve (median, 28%; IQR, 14%-48%; $P < .001$). $V_t$ also increased by a median of 30% (IQR, 7%-48%), and this change was significantly correlated with the change in dEMG amplitude ($r = 0.67$; $P < .001$). These effects were relatively stable until 120 minutes after caffeine administration. Caffeine did not consistently impact EELV, respiratory rate, or inspiratory and expiratory times.

**Conclusion** Caffeine treatment results in a rapid and sustained increase in diaphragmatic activity and $V_t$ in preterm infants. *(J Pediatr 2015;167:70-5)*.

Apnea of prematurity (AOP) is common in preterm infants of gestational age (GA) <34 weeks.[1,2] AOP may be caused by a reduced or absent inspiratory effort owing to immaturity of the brain stem (central AOP), obstruction of the (upper) airways (obstructive AOP), or a combination of the 2 factors (mixed AOP).[3] For central AOP, pharmacologic therapy with the methylxanthine caffeine is the treatment of choice.[1] The short-term effects of caffeine in preterm infants include decreased frequency of central AOP and increased minute ventilation, both of which lead to a decreased need for mechanical ventilation.[1,4] In the longer term, caffeine administration is associated with a lower incidence of bronchopulmonary dysplasia and improved neurodevelopmental outcomes at a corrected age of 18 months.[2,5]

The increase in minute ventilation following caffeine treatment is related mainly to an increase in tidal volume ($V_t$).[6-8] The mechanism by which caffeine improves $V_t$ is incompletely understood. It has been suggested that caffeine stimulates the central nervous system and improves $CO_2$ sensitivity.[4,9] Experimental studies have shown that caffeine treatment also improves contractility of the diaphragm, the major respiratory muscle in preterm infants[10-13]; however, to our knowledge, the effect of caffeine on diaphragmatic activity and its association with changes in $V_t$ have not been studied in preterm infants.

The objective of the present study was to determine the effect of a caffeine loading dose on diaphragmatic activity as measured by transcutaneous electromyography of the diaphragm (dEMG) in preterm infants. dEMG has recently been validated as a cardiorespiratory monitoring modality in preterm infants.[14] We also examined the effect of caffeine on breathing variables, including $V_t$, end-expiratory lung volume (EELV), and respiratory rate (RR). We hypothesized that a caffeine loading dose would increase diaphragmatic activity and also lead to an increase in $V_t$.

## Methods

This prospective observational cohort study was conducted at the Neonatal Intensive Care Unit of the Emma Children's Hospital, Academic Medical Center Amsterdam. We enrolled spontaneously

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| AB | Abdomen | RIP | Respiratory inductive plethysmography |
| AOP | Apnea of prematurity | RR | Respiratory rate |
| AUC | Area under the curve | $t_e$ | Expiratory time |
| dEMG | Electromyography of the diaphragm | $t_i$ | Inspiratory time |
| EELV | End-expiratory lung volume | $V_t$ | Tidal volume |
| GA | Gestational age | | |
| RC | Rib cage | | |

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breathing preterm infants of GA 26-34 weeks who were eligible for an intravenous loading dose (10 mg/kg) of caffeine base. Patients with congenital anomalies were excluded from the study. The study protocol was approved by the Institutional Review Board, and written informed consent was obtained from both parents.

Diaphragmatic activity and breathing variables were measured continuously and simultaneously from 30 minutes before until 180 minutes after administration of the caffeine loading dose (t = 0 minutes) using dEMG and respiratory inductive plethysmography (RIP). During the study period, body position and mode of respiratory support were not changed in any subject, and no nursery procedures—except feeding—were performed. In the event that any changes were necessary for clinical reasons, only recordings obtained before the change were included in the data analysis.

dEMG was recorded at the bedside using a portable 16-channel digital physiological amplifier (Dipha-16; Inbiolab, Groningen, The Netherlands). Three surface electrodes (Kendall H59P cloth electrodes; Covidien, Mansfield, Massachusetts) were placed on the chest, 2 at the costo-abdominal margin in the left and right nipple line and 1 at the height of the sternum.[14] dEMG data were digitized without analog filtering and sent wirelessly to the front end of the Dipha-16 system connected to a personal computer. One raw dEMG waveform combining the left and right diaphragmatic sides was digitally preprocessed and bandpass-filtered from 40 Hz to 160 Hz. The electrical activity of the heart was removed from the signal using the gating technique described by O'Brien.[15] This gating technique involves removal of sections of the dEMG signal centered on the QRS complex, leaving a gated dEMG. The gated dEMG was filled with a running average (ie, averaged dEMG) and used for further analysis (**Figure 1**). More details on preprocessing and postprocessing, sampling rate, filtering algorithm, and other technical aspects of the dEMG measurements are provided elsewhere.[15,16]

RIP measurements were performed by placing an elastic band (RespiBand, CareFusion, Hoechberg, Germany) around the rib cage (RC) in the nipple line and another elastic band around the abdomen (AB) just above the umbilicus. Both bands contained a Teflon-coated wire and were connected to a Bicore-II device (CareFusion, Hoechberg, Germany). An electrical oscillating signal was sent simultaneously through both wires, and the frequency modulation owing to expansion and contraction of the RC and AB bands was converted to voltage changes. The sum signal of the RC and AB bands was used to calculate an uncalibrated lung volume measurement (**Figure 1**).[17,18] RIP data were recorded in sync with the Dipha-16 data on the same personal bedside computer.

Analysis of dEMG and RIP data was performed off-line using the Polybench data acquisition and processing software package (Applied Biosignals, Weener, Germany). For these analyses, stable 30-second recordings were selected at the following fixed time points: just before (t = −5 minutes; baseline) and at 8 time points after caffeine administration (t = 5, 15, 30, 60, 90, 120, 150, and 180 minutes). A stable recording was defined as one with no (movement) artifacts in both the dEMG and RIP signals. All outcome variables were calculated automatically in Polybench using the average of all single breaths in the 30-second recording, containing approximately 30 breathing cycles.[19]

The following outcome variables were extracted from the dEMG signal. First, the amplitude, expressed in micro voltage ($\mu$V), was determined by calculating the difference between the highest (peak) and lowest (tonic) electrical activity within each breathing cycle. The average amplitude of the dEMG signal at each analysis time point after caffeine administration was expressed as the percentage change compared with baseline (%Δ dEMG amplitude). Second, diaphragmatic activity was evaluated by determining the average area under the curve (AUC) at each analysis time point in percentage change compared with baseline (%Δ AUC). Finally, RR, inspiratory time ($t_i$), and expiratory time ($t_e$) were derived from the averaged dEMG signal ($RR_{dEMG}$, $t_{i\ dEMG}$, and $t_{e\ dEMG}$). $RR_{dEMG}$ was defined as the number of peaks occurring per minute; $t_{i\ dEMG}$, as the time from the lowest activity of the diaphragm to the next maximum; and $t_{e\ dEMG}$, as the time from the maximum to the next lowest diaphragmatic activity.[20]

The analysis time points for the RIP data were identical to those for the dEMG analyses. We used the summed RIP data to calculate the average $V_t$ ($V_{t\ RIP}$) and EELV ($EELV_{RIP}$) in arbitrary units per kilogram for all time points. We next determined the percentage change in $V_t$ (%Δ $V_{t\ RIP}$) and in EELV (%Δ $EELV_{RIP}$) at each time point after caffeine administration compared with baseline.

In addition to dEMG and RIP data, we also collected the following patient data: GA, birth weight, postnatal age and weight, heart rate, and mode and settings of respiratory support.

### Statistical Analyses

Statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, New York) and Prism 5.0 (GraphPad Software, San Diego, California). Data are expressed as mean ± SD or median (IQR), depending on the distribution. Comparative analyses were conducted using repeated-measures ANOVA and the post hoc Bonferroni test or the repeated-measures Friedman and post hoc Dunns tests. Correlations between the change in diaphragmatic amplitude and $V_t$ were expressed as Pearson correlation coefficient ($r$). A $P$ value <.05 was considered statistically significant.

## Results

Thirty preterm infants (mean GA, 29.1 ± 1.3 weeks; mean birth weight, 1237 ± 370 g) were studied at a mean postnatal age of 2.7 ± 1.7 days. Twenty-five of the infants were supported by nasal continuous positive airway pressure, 4 infants were supported by nasal flow cannula, and 1 infant was without respiratory support. Respiratory mode and settings did not change during the study period. Three infants were