Diaphragmatic electromyography monitoring in preterm infants
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CHAPTER 4

The effect of caffeine on diaphragmatic activity and tidal volume in preterm infants

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ABSTRACT

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 (gestational age, 29.1 ± 1.3 weeks), most of whom were on non-invasive 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 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.

KEY WORDS
Apnea; Diaphragm; Electromyography; End-Expiratory Lung Volume; Transcutaneous
INTRODUCTION

Apnea of prematurity (AOP) is common in preterm infants with a gestational age (GA) < 34 weeks.\textsuperscript{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).\textsuperscript{3} For central AOP, pharmacological therapy with the methylxanthine caffeine is the treatment of choice.\textsuperscript{3} 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.\textsuperscript{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.\textsuperscript{2,5}

The increase in minute ventilation following caffeine treatment is related mainly to an increase in tidal volume ($V_t$).\textsuperscript{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 CO2 sensitivity.\textsuperscript{4,9} Experimental studies have shown that caffeine treatment also improves contractility of the diaphragm, the major respiratory muscle in preterm infants.\textsuperscript{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.\textsuperscript{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 in the Neonatal Intensive Care Unit of the Emma Children’s Hospital, Academic Medical Center Amsterdam. We enrolled spontaneously 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{15,16}

![Figure 1. Representative example of diaphragmatic electromyography (dEMG) and respiratory inductive plethysmography (RIP) signals. From top to bottom: raw dEMG, signal containing electrical activity of the diaphragm and the heart; gated dEMG, signal after removal of the QRS complexes; averaged dEMG, signal after filling gated dEMG with running average and used for further analysis; RIP thoracic, signal from rib cage band; RIP abdominal, signal from abdominal band; RIP sum, summed signal of RIP thoracic and RIP abdominal. Time window is 10 seconds.](image-url)
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). 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.

The following outcome variables were extracted from the dEMG signal. First, the amplitude, expressed in micro voltage (µV), 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 to baseline (% ∆ 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 to baseline (% ∆ 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 that occurred 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 then 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 (% ∆ V_{t RIP}) and in EELV (% ∆ 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 analysis**

Statistical analysis was 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 measurement ANOVA and the post hoc Bonferroni test or the repeated measures Friedman and post-hoc Dunns test. Correlations between the change in diaphragmatic amplitude and Vt 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 previously ventilated and extubated, either 6 hours (n=2) or 24 hours (n=1) before caffeine administration.

All infants tolerated the dEMG and RIP measurements well, and no electrical interference was detected during the measurements. Data were available from all 30 infants up to the 60-minute analysis time point. One infant was excluded after 60 minutes, 3 more infants were excluded after 120 minutes, and 4 more infants were excluded after 150 minutes owing to either a protocol violation (n = 1) or change in positioning (n = 7).

After the caffeine loading dose, diaphragmatic activity, expressed as the amplitude of the dEMG signal, showed a rapid (within 5 minutes) and significant increase (median 43%; IQR, 24% - 63%; P < .001) compared with baseline (Figure 2, A). This change in amplitude was caused by an increase in peak diaphragmatic activity (Table 1). Tonic activity showed a significant increase at 5 minutes after administration of the caffeine loading dose, but was similar to baseline levels at all other time points (Table 1). In line with the changes in amplitude, the median AUC of the diaphragm at 5 minutes also increased significantly (median, 28%; IQR, 14% - 48%; P < .001) compared with baseline (Table 1). The positive effect on diaphragmatic activity was relatively stable over time, although the effect seemed less pronounced during the last 60 minutes of the measurement period (Table 1 and Figure 2, A).
Table 1. Outcome variables at time points after caffeine administration and baseline

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>5 min</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
<th>150 min</th>
<th>180 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>29</td>
<td>29</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>(\Delta) AUC (%)</td>
<td>0</td>
<td>28 (14-48)***</td>
<td>17 (7-32)***</td>
<td>16 (3-37)**</td>
<td>19 (2-33)**</td>
<td>20 (6-48)***</td>
<td>25 (5-40)***</td>
<td>16 (2-35)**</td>
<td>11 (-9-25)</td>
</tr>
<tr>
<td>(\Delta) EELV (%)</td>
<td>0</td>
<td>46 (18-64)***</td>
<td>21 (14-37)</td>
<td>13 (4-43)</td>
<td>7 (4-36)</td>
<td>-16 (-59-30)</td>
<td>-7 (-68-43)</td>
<td>-5 (-75-40)</td>
<td>12 (-81-100)</td>
</tr>
<tr>
<td>Peak ((\mu V))</td>
<td>1.42 (1.21-1.92)</td>
<td>2.16 (1.68-2.66)***</td>
<td>1.98 (1.47-2.71)***</td>
<td>1.80 (1.49-2.36)***</td>
<td>1.89 (1.40-2.60)***</td>
<td>2.14 (1.51-2.50)***</td>
<td>2.16 (1.54-2.55)***</td>
<td>1.97 (1.55-2.29)***</td>
<td>1.86 (1.33-2.29)</td>
</tr>
<tr>
<td>Tonic ((\mu V))</td>
<td>0.75 (0.68-1.00)</td>
<td>1.00 (0.83-1.44)***</td>
<td>0.84 (0.69-1.14)</td>
<td>0.88 (0.73-1.03)</td>
<td>0.88 (0.67-1.09)</td>
<td>0.96 (0.75-1.28)</td>
<td>0.94 (0.81-1.18)</td>
<td>0.93 (0.76-1.16)</td>
<td>0.86 (0.70-1.12)</td>
</tr>
<tr>
<td>(t_{i\text{dEMG}}) ((\text{msec}))</td>
<td>484 ± 90</td>
<td>457 ± 72</td>
<td>466 ± 78</td>
<td>466 ± 85</td>
<td>491 ± 108</td>
<td>473 ± 81</td>
<td>447 ± 66</td>
<td>454 ± 77</td>
<td></td>
</tr>
<tr>
<td>(t_{e\text{dEMG}}) ((\text{msec}))</td>
<td>521 ± 127</td>
<td>525 ± 123</td>
<td>553 ± 185</td>
<td>500 ± 95</td>
<td>556 ± 166</td>
<td>569 ± 191</td>
<td>524 ± 124</td>
<td>500 ± 117</td>
<td>519 ± 137</td>
</tr>
<tr>
<td>RR (_{\text{dEMG}}) ((\text{min}^{-1}))</td>
<td>53 ± 10</td>
<td>57 ± 11</td>
<td>56 ± 10</td>
<td>58 ± 10</td>
<td>55 ± 11</td>
<td>57 ± 10</td>
<td>58 ± 8</td>
<td>55 ± 10</td>
<td></td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** n = number of infants, \(\Delta\) (%) = percentage change compared to baseline, AUC = area under the curve of dEMG, EELV = end-expiratory lung volume, peak = maximal electrical activity of dEMG, tonic = minimal electrical activity of dEMG, \(t_{i\text{dEMG}}\) = inspiratory time of dEMG, \(t_{e\text{dEMG}}\) = expiratory time of dEMG, RR \(_{\text{dEMG}}\) = respiratory rate of dEMG.

Data are presented in median (IQR) or in mean ± SD (°), with level of significance p < 0.001 (**), p < 0.01 (**) and p < 0.05 (*) compared to baseline.
Figure 2. The percentage change of caffeine administration on (A) diaphragmatic amplitude and (B) tidal volume over time (min), all compared with baseline. Data are presented in median (IQR) with level of significance $p < 0.001$ (***), $p < 0.01$ (**), $p < 0.05$ (*) determined with repeated measurement Friedman and post hoc Dunn’s test. $n$ = the number of infants at each analysis time point.

The increased diaphragmatic activity after caffeine administration was accompanied by a significant increase in $V_t$ compared with baseline, which was most prominent after 5 minutes (median increase, 30%; IQR, 7% - 48%; $P < .001$), followed by a gradual decrease thereafter (Figure 2, B). Using each pair of a change in dEMG amplitude and its concomitant change in $V_t$ at the 5-, 15-, 30-, and 60-minute time points for each patient (a total of 120 pairs), we constructed a scatterplot that revealed a modest but significant correlation between these 2 variables ($r = 0.67; P < .001$) (Figure 3).
Effect of caffeine on diaphragmatic activity in preterm infants

Figure 3. The relation between the change in diaphragmatic amplitude and change in tidal volume at the 5, 15, 30 and 60 minutes time point for each individual patient after caffeine administration compared to baseline. Pearson's correlation coefficient $r = 0.67$.

The EELV$_{RIP}$ showed a significant increase at 5 minutes after caffeine administration, but no differences were seen at all other time points compared with baseline (Table 1). RR$_{dEMG}$, t$_{dEMG}$ and t$_{e_dEMG}$ did not change after the caffeine loading dose (Table 1). This was also true for heart rate ($140 \pm 9$ minutes$^{-1}$) (data not shown).

DISCUSSION

Treatment with an intravenous loading dose of caffeine in preterm infants leads to a rapid and sustained increase in diaphragmatic activity. Furthermore, this increase in diaphragmatic activity seems to be associated with an increase in $V_t$. Although the present study measured only diaphragmatic electrical activity and not diaphragmatic contractility, our findings are consistent with in vivo and in vitro animal studies showing that caffeine administration augments diaphragmatic contractility.11-13 To date, only 1 published human study has assessed the effect of caffeine on diaphragmatic activity. Supinski et al10 administered an oral caffeine dose to 6 healthy adults and showed that caffeine increased transdiaphragmatic pressure, suggesting that caffeine enhances diaphragmatic muscle contractility.

The exact mechanism by which caffeine improves diaphragmatic contractility is unclear. Studies have suggested that caffeine augments contractile protein activation by increasing sarcoplasmic reticulum calcium concentration.10,21 Caffeine also may affect muscle function through the adrenal release of epinephrine, which improves diaphragmatic contractility.10 Another possibility is that caffeine has a central effect that is transmitted to the diaphragmatic muscle, leading to increased activity.

The effect of caffeine on minute ventilation has been studied only in spontaneously breathing term infants with frequent apnea6 and mechanically ventilated infants with...
bronchopulmonary dysplasia. Both studies reported a significant average increase in \( V_t \) (24% and 42%) and minute ventilation (27% and 37%) after caffeine administration. In those studies, RR, \( t_i \), and \( t_e \) did not change in response to caffeine treatment. These results are consistent with those of the present study in spontaneously breathing preterm infants, including the treatment effect on \( V_t \) (average median increase, 23% over the first 60 minutes compared with baseline).

Our simultaneous measurement of changes in diaphragmatic activity and \( V_t \) after caffeine treatment allowed us to explore a possible association between these 2 physiological variables. For this investigation, we selected all pairs of dEMG amplitude changes and \( V_t \) RIP changes during the first 4 analysis time points, because the positive effect of caffeine on these variables was relatively stable within this time frame. The significant correlation between the increase in diaphragmatic activity and the increase in \( V_t \) RIP suggests that the former is in part responsible for the caffeine-induced increase in \( V_t \).

By measuring the changes in diaphragmatic activity and \( V_t \) for 3 hours, we were able to assess the effect of caffeine administration on these variables over time compared with baseline. Our results show that diaphragmatic activity and \( V_t \) RIP increase rapidly after caffeine administration, and that these positive effects are relatively stable in terms of treatment effect over the first 120 minutes, but then apparently trend downward over the next 60 minutes. There are 2 possible explanations for this observation. First, the high peak serum levels seen shortly after the loading dose of caffeine will slowly decrease over time, which may decrease the treatment effect on diaphragmatic activity and \( V_t \) RIP. Second, over time the patient may experience subtle changes in sleep state and lung function, which also may affect diaphragmatic activity or \( V_t \) and make the direct effect of caffeine on these variables less pronounced.

We also examined the effect of caffeine on the EELV. Apart from a significant increase at 5 minutes after caffeine administration, EELV did not change at any other time point compared with baseline. Similar changes were seen in the tonic activity of the diaphragm, with a significant increase occurring only at 5 minutes after caffeine administration. These findings suggest that the increase in EELV at the 5-minute time point may have been mediated by a caffeine induced increase in tonic activity of the diaphragm, an interaction also reported in other studies; however, the fact that the increases in EELV and tonic activity were not consistent over time calls into question the clinical relevance of this finding and precludes us from drawing firm conclusions.

Interestingly, the tonic activity of the diaphragm after caffeine administration reported here is higher than that found in a previous study by Emeriaud et al (46% vs 30% or less). The patients included in that study were considerably older (mean age at measurement, 2.3 months) and supported by mechanical ventilation, however. It might well be that compared with this population, spontaneously breathing preterm infants need more tonic activity of the diaphragm to stabilize EELV.
This study has several limitations that must be addressed. First, our observational study did not include a placebo group, because we did not want to postpone caffeine treatment in this vulnerable population. Our finding of rapid increases in both diaphragmatic activity and \( V_t \) after caffeine treatment in all infants strongly suggests that these effects are truly caused by caffeine. Second, we did not measure sleep state before, during, and after our study period. Changes in sleep state also can affect diaphragmatic activity and \( V_t \).\textsuperscript{22,23} Third, the increases in dEMG may be caused in part by activity of other adjacent muscles, a phenomenon known as cross-talk; however, previous studies have shown that cross-talk of the intercostal and/or abdominal muscles during dEMG in newborn infants is of limited importance.\textsuperscript{16,25} Finally, this study measured changes in dEMG and \( V_{t,\text{RIP}} \) only during the 3 hours after a caffeine-loading dose. In most cases, caffeine maintenance doses are administered every 24 hours. Whether the beneficial effects of caffeine on dEMG and \( V_{t,\text{RIP}} \) will last for 24 hours cannot be determined by the present study; a longer measurement period would be required. Such a study also would need to take into account the fact that a patient’s clinical condition almost certainly will change over a 24-hour study period, which also can affect dEMG and \( V_{t,\text{RIP}} \) values.\textsuperscript{22}

In conclusion, our study adds important information on the mechanism of caffeine’s effects in preterm infants. First, it confirms that caffeine treatment, through an increase in diaphragm activation, also leads to an increase in \( V_t \) in preterm infants. Second, it shows that caffeine results in an increase in diaphragmatic activity, and that this may be part of the underlying mechanism for the positive effect on \( V_t \). Third, this positive effect of caffeine on diaphragmatic activity and \( V_t \) occurs within minutes after administration. These findings suggest that there likely is also an indication to start caffeine treatment in patients with hypoventilation rather than true AOP. Our study also demonstrates the potential of transcutaneous dEMG in preterm infants. In addition to providing basic monitoring of RR and heart rate in preterm infants,\textsuperscript{14} it also is capable of detecting changes in diaphragmatic activity, which are closely correlated to the diaphragmatic work of breathing.\textsuperscript{26} Future studies are needed to investigate this potential benefit of dEMG monitoring in preterm infants.

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REFERENCES


