Effects of Caffeine in Lung Mechanics of Extremely Low Birth Weight Infants

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Abstract

Objective: To investigate the effect of caffeine citrate (methyxanthine) on the pattern of breathing and lung mechanics in extremely low birth weight (ELBW) infants with apnea of prematurity (AOP), during mechanical ventilation and following extubation while breathing spontaneously.

Methods: In this pilot prospective observational study 39 ELBW infants were monitored: Twenty AOP - diagnosed with respiratory distress syndrome (RDS) - and 19 controls. Infants with AOP were assessed on mechanical ventilation before caffeine administration and immediately after extubation which occurred at 11-14 days post- caffeine citrate commencement. Control infants were compared to the post- caffeine group. Breathing pattern parameters, lung mechanics and work of breathing were assessed.

Results: Caffeine citrate seemed to markedly increase Tidal Volume ($V_T$) in the post caffeine group when compared to the control group (7.3 ± 2.0 ml/kg and 5.7 ± 1.5 ml/kg respectively) and slightly decreased breathing rate (64 ± 17 and 70 ± 19 breaths/min), respectively. Minute Ventilation ($V_e$) and Expiratory Time ($T_e$) increased (P<0.001) and Total Breathing Time ($T_{TOT}$) also increased (P=0.187) but caffeine did not seem to have an effect on Inspiratory Time ($T_i$) (P=0.09). Subsequently, Time Cycle ($T_i/T_{TOT}$) decreased (P<0.001). Work of Breathing ($W$) also increased (P=0.001).

Conclusions: These findings advocate that administration of caffeine citrate in ELBW infants with AOP increased $V_T$, although this occurred at the cost of an elevated W. The long-term effects of caffeine on lung function were positive (following administration every 24 hours at 5 mg/kg) after a period of 11-14 days PCA from the initial administration of the drug.

Keywords: Lung Function, Premature Infants, Mechanical Ventilation, Caffeine Citrate, Apnea

Introduction

In the vast majority of the ELBW (< 1000 gr) infants, the immediate post-natal days may be complicated by one or several acute respiratory disorders (RDS, Wilson-Milky syndrome or pneumonia). Assisted ventilation is usually instituted during the first day of life because of significant respiratory failure and progressive abnormalities in blood gases [1]. With growth and maturation of these ELBW infants, the ventilatory assistance diminishes, but, during the weaning phase, recurrent central apneic and/or bradycardia periods may occur, usually, in the post-conceptional age (PCA) of 28 - 33 weeks. The apneic episodes are associated with bradycardia, cyanosis, changes in muscle tone, hypoxemia and hypoventilation. The AOP normally diminishes in number and frequency with further maturation, such that resolution of the problem tends to occur at approximately 34 to 36 wk PCA. It is estimated that at least 50% of the surviving ELBW infants have such apneic episodes [2]. Moreover, with episodes of > 20s duration, there is a greater incidence of intraventricular hemorrhage (IVH) and hydrocephalus as well as abnormal neurological development during the first year of life, compared to non apneic preterm infants [3].

It is demonstrated that caffeine, as respiratory stimulant, is a pharmacologic agent that handles AOP in infants by increasing the respiratory center neural output as well as the chemoreceptor sensitivity to carbon dioxide [4,5]. Such an effect on the respiratory center may result in an increased frequency rate and/or tidal volume [6], the precise way in which respiratory stimulation is achieved may have important
consequences for the work of breathing, which subsequently is required to generate a given alveolar minute ventilation [7-10]. Moreover, a marked increase of the work of breathing in an infant whose gas exchange is already compromised may increase the risk of fatigue and increase the weaning period. The purpose of our pilot prospective observational study, as initially designed [11] and conducted throughout, was to analyze if caffeine citrate increased ventilation in ELBW infants diagnosed with AOP by examining the caffeine effects on breathing frequency, tidal volume, lung mechanics, and work of breathing.

Materials and Methods

Patient population

In this pilot prospective observational study we tested 39 ELBW infants divided into 2 groups (Table 1). Twenty of them - comprising Group Caffeine were diagnosed with neonatal lung disease and AOP. Definition of AOP was made as per the American Academy of Pediatrics Policy Statement [12]. Infants with other diagnoses that could be contributory to the apnea (significant CNS hemorrhage, infection, metabolic derangement, patent ductus arteriosus or cardiovascular structural abnormalities) or other conditions (VHI, hydrocephalus) that could have contributed to differences in neural control or respiration were specifically excluded from the study. All infants in Group Caffeine had been diagnosed with a severe RDS within the first hours following birth. RDS in these infants was progressively deteriorating to the condition of bronchopulmonary dysplasia (BPD) defined: 1) by the persisting requirement for supplemental oxygen beyond 28 days following mechanical ventilation for a minimum of 14 days for respiratory failure - PaO₂ < 60 torr and PaCO₂ > 50 torr in room air; and 2) by an abnormal chest radiograph. All had signs of symptomatic AOP - defined as episodes of SaO₂ < 85% and/or bradycardia - requiring tactile stimulation and higher inspired oxygen for recovery, on more than 6 occasions within the 24-hour period prior to the first lung mechanic measurements and caffeine administration. All infants were ventilated with Draeger Babylog-8000 at SIMV mode. Lung mechanics of these 20 infants were studied at two different time periods: 1) under mechanical ventilation, before administration of caffeine (Group Caffeine: PCA: 30.3 ± 1.5 wk and body weight: 787 ± 207 gr), and 2) after extubation, while breathing spontaneously, at 11-14 days after commencement of caffeine (Group Caffeine post: PCA: 31.8 ± 1.4 wk and body weight: 1032 ± 228 gr). Successful extubation from mechanical ventilation of these infants was attained through permissive hypercapnia, maintaining a PaCO₂ < 60, pH ≈ 7.28, SaO₂ > 92%. Subsequently, none of these infants showed any clinical evidence of upper airway obstruction following extubation (i.e. stridor; witnessed obstructive apnea - chest wall movement in the absence of oro-nasal airflow). Group Control consisted of the 19 neonates (gestation age at birth: 26.3 ± 2.3 wk and birthweight: 1009 ± 458 gr), who showed no clinical manifestations of respiratory problems, always breath spontaneously (never intubated), without apnea episodes - thus not receiving any respiratory stimulant treatment; these infants were detained in the NICU until their successful maturation would be ensured. The lung function of these 19 infants (Group Control) was assessed at PCA: 31.2 ± 0.8 wk and body weight: 1167 ± 430 gr. Subjects were inborn and managed in the NICUs of the Royal Victoria Hospital - McGill University Health Center, Sainte-Justine Hospital - University of Montreal, and, Children’s Hospital Los Angeles - Keck School of Medicine.

Interventions and measurements

In the 20 infants of first group, Caffeine Citrate (Roxane Laboratories, Columbus, OH) was administered at 10 mg/kg loading dosage [4] and subsequently every 24 hours at 5 mg/kg. Caffeine concentration in blood serum was measured 3 times, in total, per subject, that is: within 24 hours from the commencement of the drug, 5-7 days following the commencement and immediately after extubation (11-14 days following commencement). The caffeine concentration level in blood serum measured for subjects of Group Caffeine throughout the study period was 51 ± 26 µM (Average ± SD).

Airway opening pressure (P₀) was recorded with a Validyne MP-45 ± 50 cmH₂O pressure transducer. A water-filled 8-FG esophageal catheter and pressure transducer (Sanborn 268) was utilized to record the esophageal pressure (Pₑ) [13]. The optimal positioning of the catheter was determined through occlusion [13] such that the excursions in P₀ and Pₑ were equal during an occluded breath. The airflow (V) was recorded with a Fleish #1 pneumotachograph attached to a Validyne MP-45 ± 2 cmH₂O pressure transducer. After the attending Neonatologist ordered full extubation, lung mechanics was measured: the pneumotachograph was connected to a facemask which in turn was adapted to the subject. To avoid inadvertent hypoxemia during this short period, a constant gas flow of at least 35% ḞO₂ was provided throughout the circuit and adapted to SaO₂.

During the time of stable spontaneous breathing - for subjects in both Groups Caffeine and Control - a one minute epoch of regular quiet breathing was captured at 100Hz sampling frequency using the DATALAB data acquisition program [14] and stored on a personal computer for subsequent analysis. All breaths, individually for each subject, indicated a reproducible spontaneous breathing pattern maintaining a stable (= ±5% variability) tidal volume normalized to body weight (ml/kg).

The Institutional Review Boards approved this study. Informed consent was obtained from parents. The administration of caffeine citrate for respiratory stimulation was the decision of the attending Neonatologist as part of the treatment regime instituted for symptomatic AOP.

Lung function analysis

The analysis of breathing pattern and the calculation of lung...
variables in all groups were tested for normality. Failure to satisfy the normality hypothesis suggested use of non-parametric statistics. Therefore, to compare the distributions of each one of the lung function variables between pre- (Group Caffeine pre) and post-caffeine (Group Caffeine post) groups as well as between post-caffeine (Group Caffeine post) and Group Control, we used the Kolmogorov-Smirnov (KS) non-parametric test. Sample size calculations were performed according to Mann-Whitney Inequality Test.

**Results**

Lung function parameters pre- and post- Group Caffeine as well as for the Group Control, are listed in Table 2. All volume-related variables (VT, VT/TI, f/VT, EL, RL, ZL and W) were normalized to body weight. Both PCA and body weight before and after the initiation of caffeine therapy (Groups Caffeine pre vs Caffeine post) differed significantly (p<0.001, t-test). However, there was no statistical significant difference in PCA (p=0.43, t-test) and body weight (p=0.27, t-test) between the Groups Caffeine post and Control.

Administration of caffeine citrate resulted in marked increases in VT, and slight decrease in TE, when Groups Caffeine and Control were compared. The timing of the breathing pattern (associated to caffeine administration) TE and TTOT were increased (so that f was decreased) while TI was decreased. This decreased the TI/TTOT ratio. There was an increase in W with caffeine. The ratio f/VT, previously described as a reflection of respiratory insufficiency [16-18], was also diminished by caffeine (Figure 1).

Control infants were breathing at a higher f but at a substantially lower VT and VE than the comparable - in terms of maturation - Caffeine post infants. This resulted in a concomitant decrease in the VT, and VE relative to the comparable - in terms of maturation - Caffeine post infants. Mean inspiratory flow (VT/TI) was also lower. However, although Ptp, EL and ZL were comparable in both groups, a substantially lower RL and W was noted in the Control infants (Figure 2).

Dynamic compliance Cc was computed as $C_c = \frac{1}{E_c}$.

**Statistical analysis**

We used Student’s t-test to compare the PCA and body weight between the children at the post- Caffeine group (Group Caffeine post) and Group Control. The distributions of lung function parameters, individually per patient, was performed through the ABREATH Respiratory Data Analysis Module of ANADAT [15] as follows:

1. First, respiratory flow ($\dot{V}$) was numerically integrated to give volume (V) after adjusting the baseline in $\dot{V}$ to remove the net baseline drift in $\dot{V}$.
2. Tidal volume (VT) was then calculated for each breath as the total volume excursion in V between adjacent end-expiratory points.
3. Expiratory time (TE) and inspiratory time (TI) were calculated as the time taken by V for each breath to proceed from its peak value to its minimum, and vice versa, respectively.
4. Lung resistance (RL) and elastance (EL) were derived by fitting the equation:

$$P_{tp} = [E_L \cdot V] + [R_L \cdot \dot{V}] + P_0$$

where $P_0$ is an estimate of the positive end-expiratory pressure (PEEP).

5. The magnitude of impedance (ZL) was calculated through the Coates et al [5] formula $Z_L = \sqrt{\frac{1}{\omega C_L} + R_L^2}$

where $\omega = 2\pi f$, f=breathing frequency (per patient), $\pi = 3.14159$.

6. The work of breathing per minute (W) was calculated by the Otis et al. [16] formula $W = \frac{1}{2IC_L} + \frac{R_L^2}{4}$. Dynamic compliance Cc was computed as $C_c = \frac{1}{E_c}$.

**Figure 1**

![Figure 1: Distribution (Average ± SD) of f and VT at 48 hours pre- (Group Caffeine pre) and 11-14 days post- (Group Caffeine post) caffeine commencement respectively as well as in Group Control.](image-url)
Discussion

This pilot prospective observational study examined the effect of caffeine citrate to the lung function of premature infants with idiopathic AOP. A significant increase in $V_T$ and a significant increase in $W$ were noted. These changes were independent of the maturation effect that would otherwise be expected due to the changes in PCA at the post-caffeine phase. Indeed, control infants at comparable PCA had a substantially lower $V_T$, being achieved at modest $W$ levels.

The increase in post-caffeine $V_T$ occurred through a clinically significant increase in $V_{in}$ in contrast to a minor decrease in respiratory frequency (Table 2). This finding indicates that the effect of caffeine, observed at about 3 half-lives following the commencement of the drug, is different than the effect monitored shortly after the commencement, i.e. improved ventilation with minimal increase in frequency [13,19]. Whilst we found a statistically significant change in respiratory frequency, the magnitude of this change is likely of little clinical importance. Our own studies [20] have demonstrated that after 3 half-lives (11-14 days approximately), caffeine may increase central respiratory drive (assessed in terms of $P_{0.1}$), in agreement with the results of Rigatto et al. [21]. Moreover, our present study also suggests that within the same period, respiratory drive - expressed through the mean inspiratory flow ($V_{in}$) - increases significantly with caffeine (Table 2). This increase is accentuated by the fact that normal infants had a substantially lower respiratory drive within the period in question.

The mechanical properties of the lungs also changed with time in the Group Caffeine, with the magnitude of mechanical impendence decreasing significantly (Table 2). This was due to a reduction in both $R_L$ and $E_L$. Both $R_L$ and $E_L$ changed with breathing frequency, but in opposite directions [22], so the slight change in $f$ we observed could not have caused the changes in mechanical parameters. A more likely explanation would be the increase in $V_{in}$ - which has been shown to produce a decrease in both $R_L$ and $E_L$ [22] possibly due to opening of closed peripheral lung units corresponding to an improvement of the lung disease [23]. This latter explanation is sustained by the natural course of RDS in premature neonates.

It would also appear that the effects of caffeine in our study coincided with those observed by Laubscher [24] after 7 days of commencement. Using a different technique of measurement in 53 infants, they demonstrated an increase in $C_{vital}(0.71$ to $1.33 \text{ mL/cmH}_2\text{O/kg}$), albeit of a different magnitude. However, we found a considerably higher $E_L$ at baseline (Group Caffeine) than they did, possibly reflecting: 1) lower gestational age at birth, 2) more severe parenchymal lung disease at initial study, 3) differences in the study periods introducing divergent maturational characteristics. Furthermore, Laubscher et al. [24] measured the compliance of the total respiratory system in contrast to lung compliance.

Our Group Caffeine post fully extubated from mechanical ventilation at a period varying from 11 to 14 days from the commencement of caffeine, thus post-caffeine measurements were correspondingly captured at approximately after 3 half-lives. Although within this period changes in the BPD disease-state might occur, these would be of a limited magnitude, resulting in rather minimal or no effect on the mechanical properties of the lung [25,26] as illustrated by our own control infants at the same PCA. It is also inherent, in the data presented, that although $E_L$ decreased from 2.52 to 0.93 cmH$_2$O/mL/kg, this was at the lower end of the values for normal children. In addition, the $R_L$ remained abnormally elevated at $> 100 \text{ cmH}_2\text{O/L/s/kg}$, suggesting that the mechanical function was not consistent with healed BPD [27]. Similarly, alterations of central/respiratory drive were noted within the same period. However, in contradiction to this concept there was no change in the respiratory rate (if decreased from 68.1 to 64.3 breaths/min) and that at both periods pre- and post-caffeine commencement, the children had a period of at least 1 minute of normal spontaneous breathing. In addition, comparison with 19 infants in Group Control clearly indicated the extent of the maturation effects, appearing due to our study design, i.e. the pre- and post-caffeine periods were selected 13 to 16 days apart. Furthermore, consistency in care for both Groups Caffeine and Control (e.g. no diuretics or change in other therapy) ensured the unbiased function of the lung system within the study period.

Also, $W$ was lower in the Group Caffeine pre when compared to Caffeine post probably because these infants were on mechanical ventilation (before the Group Caffeine pre was disconnected to...
breath spontaneously for 1 min). The difference in W between Groups Caffeine\textsubscript{post} and Control suggested that the stimulation of the central nervous system resulted in an increase in muscular tone. Despite this increase in W, body weight differences between the two groups was not statistically significant suggesting that the increase in work of breathing observed in the Group Caffeine\textsubscript{post} did not impair the infant growth.

Furthermore, due to the baseline characteristics of the study population as well as the nature of the intervention on study subjects, this pilot prospective observational study was difficult to conduct, hence the limited sample size. As a result, we only recruited 20 subjects (Group Caffeine). Nevertheless, the 1 minute of breathing pattern we recorded for each patient, expressed a reproducible periodic breathing within the observational period; thus, we feel that our recording was adequate [28]. Even more so, in Group Control we recruited 19 only infants. However, it was even more difficult to find a comparative arm free from apnea and other respiratory complications. It is noted that we checked all lung function variables for potential statistical skewing of their frequency distributions. Once stability was ensured, comparisons between the Group Caffeine\textsubscript{post} and Control were performed on frequency distributions. Once stability was ensured, comparisons were performed on frequency distributions. Once stability was ensured, comparisons were performed on frequency distributions.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>-95%CI</th>
<th>+95%CI</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>StdDev</th>
<th>P, Caffeine\textsubscript{post} vs Control</th>
<th>P, Caffeine\textsubscript{pre} vs Control</th>
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<tbody>
<tr>
<td>V\textsubscript{L} (ml/kg)</td>
<td>5.226</td>
<td>5.063</td>
<td>5.388</td>
<td>5.067</td>
<td>1.377</td>
<td>10.883</td>
<td>1.450</td>
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<td>T\textsubscript{T} (s)</td>
<td>0.529</td>
<td>0.509</td>
<td>0.549</td>
<td>0.470</td>
<td>0.160</td>
<td>1.160</td>
<td>0.176</td>
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<td>T\textsubscript{TTOT} (s)</td>
<td>0.598</td>
<td>0.561</td>
<td>0.634</td>
<td>0.550</td>
<td>0.270</td>
<td>1.730</td>
<td>0.223</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T\textsubscript{I} (s)</td>
<td>0.507</td>
<td>0.473</td>
<td>0.542</td>
<td>0.430</td>
<td>0.280</td>
<td>1.860</td>
<td>0.221</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>T\textsubscript{TOT} (s)</td>
<td>0.446</td>
<td>0.426</td>
<td>0.466</td>
<td>0.380</td>
<td>0.220</td>
<td>1.140</td>
<td>0.178</td>
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<td>0.321</td>
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<tr>
<td>T\textsubscript{I} / T \textsubscript{TOT}</td>
<td>0.409</td>
<td>0.387</td>
<td>0.432</td>
<td>0.380</td>
<td>0.180</td>
<td>1.060</td>
<td>0.139</td>
<td>&lt;0.001</td>
<td>0.088</td>
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<td>V\textsubscript{T} (ml/kg) / (s)</td>
<td>0.446</td>
<td>0.447</td>
<td>0.461</td>
<td>0.448</td>
<td>0.202</td>
<td>0.659</td>
<td>0.062</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>V\textsubscript{T} (ml/min)</td>
<td>13.001</td>
<td>12.484</td>
<td>13.519</td>
<td>12.922</td>
<td>3.862</td>
<td>27.787</td>
<td>4.614</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>f (breaths/min)</td>
<td>0.595</td>
<td>0.892</td>
<td>1.015</td>
<td>0.820</td>
<td>0.550</td>
<td>3.210</td>
<td>0.391</td>
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<td>&lt;0.001</td>
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<tr>
<td>fV\textsubscript{T} (Hz) / (ml/kg)</td>
<td>0.542</td>
<td>0.478</td>
<td>0.670</td>
<td>0.520</td>
<td>0.270</td>
<td>1.730</td>
<td>0.223</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>V\textsubscript{L} (ml/min)</td>
<td>3.473</td>
<td>3.304</td>
<td>3.630</td>
<td>3.496</td>
<td>1.130</td>
<td>7.260</td>
<td>2.404</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>P (cmH\textsubscript{O}2)</td>
<td>9.345</td>
<td>8.967</td>
<td>9.723</td>
<td>8.940</td>
<td>3.080</td>
<td>28.300</td>
<td>3.373</td>
<td>0.001</td>
<td>0.708</td>
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<tr>
<td>R\textsubscript{L} (cmH\textsubscript{O}2/Ls) / kg</td>
<td>123.751</td>
<td>115.056</td>
<td>132.447</td>
<td>133.938</td>
<td>0.889</td>
<td>562.000</td>
<td>77.555</td>
<td>0.248</td>
<td>&lt;0.001</td>
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<td>E\textsubscript{O} (cmH\textsubscript{O}2/ml/kg)</td>
<td>0.935</td>
<td>0.894</td>
<td>0.977</td>
<td>0.968</td>
<td>0.100</td>
<td>1.677</td>
<td>0.253</td>
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<td>0.138</td>
</tr>
<tr>
<td>Z\textsubscript{L} (cmH\textsubscript{O}2/Ls) / kg</td>
<td>335.811</td>
<td>311.809</td>
<td>359.813</td>
<td>280.479</td>
<td>1.719</td>
<td>895.347</td>
<td>214.075</td>
<td>0.682</td>
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<td>W (gr/cm/s) / kg</td>
<td>24.904</td>
<td>22.702</td>
<td>27.107</td>
<td>23.026</td>
<td>0.328</td>
<td>157.397</td>
<td>19.646</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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breath spontaneously for 1 min). The difference in W between Groups Caffeine\textsubscript{post} and Control suggested that the stimulation of the central nervous system resulted in an increase in muscular tone. Despite this increase in W, body weight differences between the two groups was not statistically significant suggesting that the increase in work of breathing observed in the Group Caffeine\textsubscript{post} did not impair the infant growth.
a positive effect of caffeine. In terms of sample size calculations based on our primary finding i.e. $\frac{V_t}{f} \geq 1.5$ (Control), at alpha level=0.1 the power of comparison is at 0.88 provided that as per allocation ratio 1:1 the sample size is $n=40$ (total, equally distributed) according to Mann-Whitney Inequality Test. Overall, the observational nature of this research, as well as differences in the Caffeine and Control Groups, constituted limitations of the study. Yet, the crude findings of this work were sufficiently indicative of the efficacy of the effect of caffeine on the lung function measured after extubation, as opposed to the lung function of a comparable control group at the same PCA.

A significant amount of work has been published the past decade focusing on the effect of caffeine in premature infants with AOP [29-64]. We feel that more work is needed on the actual mechanics of breathing through a randomized clinical trial. However, due to the challenge in performing similar studies we intended through this pilot to provide a reference towards planning for a future clinical trial. We state that for practical reasons we did not evaluate our subjects [65] in a sleep-state and note that the breathing pattern of each infant we recorded was regular, rhythmic and reproducible (i.e. stable tidal breath), while each infant was quiet but alert during wakefulness. Finally, our results cannot be extrapolated to post-term apnea, which may have a very different etiology and mechanism than AOP.

Given these beneficial effects of caffeine on $\frac{V_t}{f}$ in the premature infant, there is a need to evaluate the efficacy of this drug in other groups of patients. So far, this effect has been effective in term infants with brief central apneas and desaturation. However, because of its respiratory stimulatory effects [66], caffeine should be reconsidered as a central respiratory stimulant to facilitate weaning from mechanical ventilation in older patients with ARDS or febrile neutropenia. Given the variability of metabolism of caffeine in different age groups [66,67] monitoring of drug concentration to ensure a therapeutic blood level should be part of this evaluation.

Summarizing, administration of caffeine citrate in ELBW infants increased $\frac{V_t}{f}$ but at the cost of an elevated $R_L$ and $W$. The results from this pilot study warrant further investigation through a large clinical trial to explore whether caffeine may effectively assist in the prompt and gradual decrease of mechanical ventilatory support in ELBW infants possibly shortening the course of weaning.

Notable Remark

Our thoughts go to Dr. G. Michael Davis (deceased 08/29/2008), a friend, a teacher, a mentor, an inspiration to us all.

Abbreviations Used (in order of appearance)

- ELBW: Extremely Low Birth Weight
- AOP: Apnea of Prematurity
- RDS: Respiratory Distress Syndrome
- VT: Tidal Volume
- f: Breathing Frequency/Rate
- $f/V_t$: Rapid Shallow Breathing Index
- $V_t$: Minute Ventilation
- $T_e$: Expiratory Time
- $T_{TOT}$: Total Breathing Time
- $T_i$: Inspiratory Time
- $T_{TOT}/T_i$: Time Cycle
- $W$: Work of Breathing
- PCA: Post-Conceptional Age
- BPD: Bronchopulmonary Dysplasia
- IVH: Intraventricular Hemorrhage
- $\text{PaO}_2$: Partial Pressure of O2 in arterial blood
- $\text{PaCO}_2$: Partial Pressure of CO2 in arterial blood
- $P_{ao}$: Airway Opening Pressure
- $P_{es}$: Esophageal Pressure
- $V$: Respiratory Volume
- $\text{FiO}_2$: Fraction of Inspired Oxygen
- $\text{SaO}_2$: Oxygen Saturation
- NICU: Neonatal Intensive Care Unit
- $R_L$: Lung Resistance
- $E_L$: Lung Elastance
- $P_{tp}$: Transpulmonary Pressure = $P_{ao}$ - $P_{es}$
- $Z_L$: Impedance
- $C_L$: Dynamic Lung Compliance
- $C_{RS}$: Dynamic Respiratory Compliance

References


