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-Mikity 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. As the mechanical properties of the lung depend upon frequency and tidal volume [6], the precise way in which respiratory stimulation is achieved may have important

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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 (IVH, 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 - $PaO_2 < 60$ torr and $PaCO_2 > 50$ torr in room air, and 2) by an abnormal chest radiograph. All had signs of symptomatic AOP - defined as episodes of $SaO_2 < 85\%$ 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$_{pre}$, 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 hypercapnea, maintaining a $PaCO_2 < 60$, pH ≈ 7.28, $SaO_2 > 92\%$. 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 (P_{ao}) was recorded with a Validyne MP-45 ± 50 cmH$_2$O pressure transducer. A water-filled 8-FG esophageal catheter and pressure transducer (Sanborn 268) was utilized to record the esophageal pressure (P_{es}) [13]. The optimal positioning of the catheter was determined through occlusion [13] such that the excursions in P_{es} and P_{ao} were equal during an occluded breath. The airflow ($\dot{V}$) was recorded with a Fleisch #1 pneumotachograph attached to a Validyne MP-45 ± 2 cmH$_2$O 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% F_iO_2 was provided throughout the circuit and adapted to SaO_2.

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

	Group Caffeine (n=20)	Group Control (n=19)	P
Gestational Age at Birth (weeks)	25.2 ± 1.3	26.3 ± 2.3	0.34
Birth weight (gr)	638 ± 106	1009 ± 458	<0.001
PCA at study on mechanical ventilation, before caffeine administration (days)	30.3 ± 1.5	-	-
Weight at study on mechanical ventilation, before caffeine administration (gr)	787 ± 207	-	-
PCA at study in spontaneous breathing (days)	31.8 ± 1.4	31.2 ± 0.8	0.43
Weight at study in spontaneous breathing (gr)	1032 ± 228	1167 ± 430	0.27

Table 1: Patients' characteristics. Statistical comparisons between the two groups were performed with a Student's t-test.

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mechanics 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 V.

2. Tidal volume (V_T) was then calculated for each breath as the total volume excursion in V between adjacent end-expiratory points.

3. Expiratory time (T_E) and inspiratory time (T_I) 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 (R_L) and elastance (E_L) were derived by fitting the equation:

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

to measurements of P_{tp} (transpulmonary pressure = $P_{ao} - P_{es}$) where P_0 is an estimate of the positive end-expiratory pressure (PEEP).

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

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

6. The work of breathing per minute (W) was calculated by the Otis et al. [16] formula $W = \left(\frac{1}{2fC_L} + \frac{R_L}{4}\pi^2\right)V_E^2$.

Dynamic compliance C_L was computed as $C_L = \frac{1}{E_L}$.

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 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 Cafeine$_{pre}$) 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 (V_T, V_T/T_I, f/V_T, E_L, R_L, Z_L 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 V_T, and slight decrease in T_E, when Groups Caffeine and Control were compared. The timing of the breathing pattern (associated to caffeine administration) T_E and T_{TOT} were increased (so that f was decreased) while T_I was decreased. This decreased the T_I/T_{TOT} ratio. There was an increase in W with caffeine. The ratio f/V_T, 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 V_T and V_E than the comparable - in terms of maturation - Caffeine$_{post}$ infants. This resulted in a concomitant increase of the f/V_T index. T_{TOT} was also comparable albeit of unequal T_I and T_E periods, resulting in a higher T_I/T_{TOT} cycle than the Caffeine$_{post}$ infants. Mean inspiratory flow (V_T/T_I) was also lower. However, although P_{tp}, E_L and Z_L were comparable in both groups, a substantially lower R_L and W was noted in the Control infants (Figure 2).
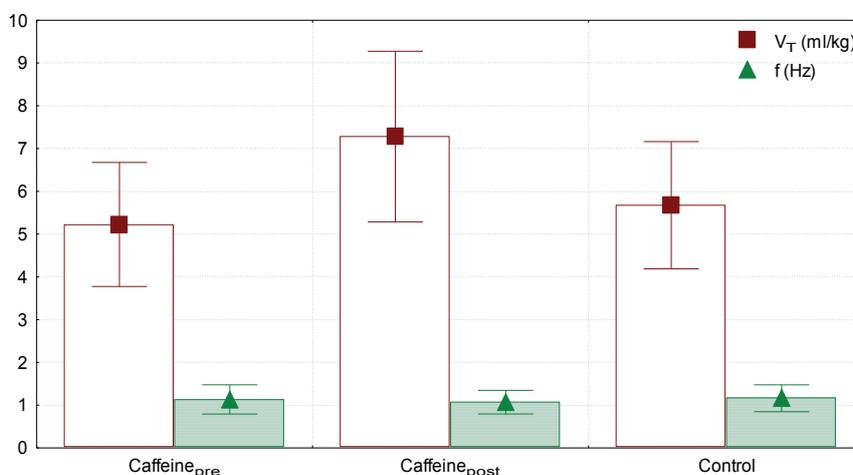

Figure 1: Distribution (Average ± SD) of f and V_T at 48 hours pre- (Group Caffeine$_{pre}$) and 11-14 days post- (Group Caffeine$_{post}$) caffeine commencement respectively as well as in Group Control.

Figure 2: Distribution (Average ± SD) of R_L, Z_L and W at 48 hours pre- (Group Caffeine$_{pre}$) and 11-14 days post- (Group Caffeine$_{post}$) caffeine commencement respectively as well as in Group Control.
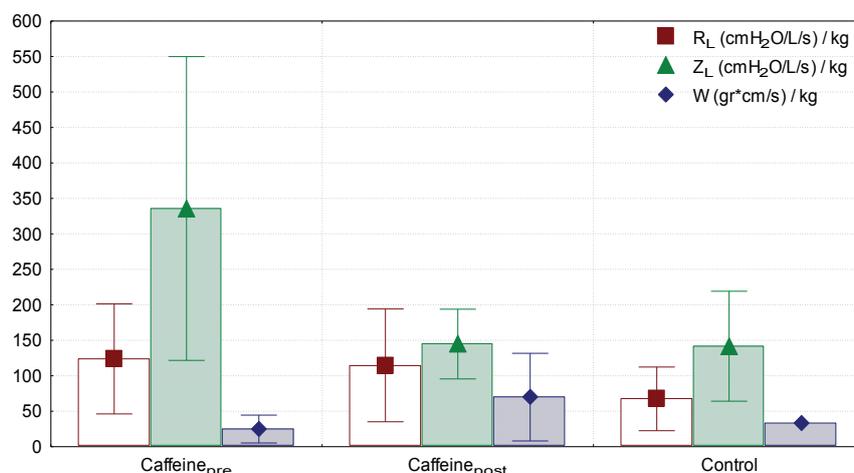
Discussion

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_E 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_E being achieved at modest W levels.

The increase in post- caffeine V_E occurred through a clinically significant increase in V_T, 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_T/T_I) - 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 impedance 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_T - 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_{RS} (0.71 to 1.33 mL/ cmH$_2$O/kg), albeit of a different magnitude. However, we found a considerably higher E_L at baseline (Group Caffeine$_{pre}$) 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 divert 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 cmH$_2$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 (f 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

		Mean	-95%CI	+95%CI	Median	Min	Max	StdDev	P, Caffeine$_{pre}$ vs Control	P, Caffeine$_{post}$ vs Control
V_T (ml/kg)	Caffeine$_{pre}$	5.226	5.063	5.388	5.067	1.377	10.883	1.450	<0.001	
	Caffeine$_{post}$	7.282	6.957	7.607	6.832	2.859	12.023	1.995		<0.001
	Control	5.676	5.442	5.910	5.501	2.539	10.612	1.488		
T_E (s)	Caffeine$_{pre}$	0.529	0.509	0.549	0.470	0.160	1.160	0.176	<0.001	
	Caffeine$_{post}$	0.598	0.561	0.634	0.550	0.270	1.730	0.223		<0.001
	Control	0.507	0.473	0.542	0.430	0.280	1.860	0.221		
T_I (s)	Caffeine$_{pre}$	0.446	0.426	0.466	0.380	0.220	1.140	0.178	0.030	
	Caffeine$_{post}$	0.409	0.387	0.432	0.380	0.180	1.060	0.139		0.088
	Control	0.446	0.411	0.480	0.390	0.240	1.990	0.220		
T_{TOT} (s)	Caffeine$_{pre}$	0.975	0.938	1.012	0.855	0.410	1.960	0.329	0.321	
	Caffeine$_{post}$	1.007	0.956	1.057	0.920	0.480	2.630	0.310		0.187
	Control	0.953	0.892	1.015	0.820	0.550	3.210	0.391		
T_I/T_{TOT}	Caffeine$_{pre}$	0.454	0.447	0.461	0.448	0.202	0.659	0.062	<0.001	
	Caffeine$_{post}$	0.412	0.398	0.425	0.396	0.275	0.700	0.082		<0.001
	Control	0.466	0.456	0.477	0.460	0.276	0.742	0.068		
V_T / T_I (ml/kg) / (s)	Caffeine$_{pre}$	13.001	12.484	13.519	12.922	3.862	27.787	4.614	<0.001	
	Caffeine$_{post}$	19.696	18.368	21.023	18.790	4.168	39.459	8.145		<0.001
	Control	14.168	13.377	14.958	13.395	3.585	26.846	5.032		
f (breaths/min)	Caffeine$_{pre}$	68.1	65.8	70.4	70.2	30.6	146.3	20.5	0.047	
	Caffeine$_{post}$	64.3	61.6	67	65.2	22.8	125	16.6		0.008
	Control	69.7	66.7	72.7	73.2	18.7	109.1	18.8		
f/V_T (Hz) / (ml/kg)	Caffeine$_{pre}$	0.241	0.226	0.256	0.234	0.071	1.482	0.130	<0.001	
	Caffeine$_{post}$	0.159	0.148	0.170	0.139	0.042	0.467	0.068		<0.001
	Control	0.222	0.208	0.236	0.216	0.042	0.547	0.090		
V_E (ml/min)	Caffeine$_{pre}$	347.373	334.042	360.705	349.463	113.580	726.404	118.904	<0.001	
	Caffeine$_{post}$	471.154	442.036	500.271	475.980	153.173	799.831	178.627		<0.001
	Control	386.515	367.531	405.498	377.882	132.037	690.313	120.808		
$\Box P$ (cmH$_2$O)	Caffeine$_{pre}$	9.345	8.967	9.723	8.940	3.080	28.300	3.373	0.001	
	Caffeine$_{post}$	10.618	9.895	11.341	10.250	3.170	31.620	4.435		0.708
	Control	10.412	9.612	11.212	8.995	2.960	24.600	5.090		
R_L (cmH$_2$O/L/s) / kg	Caffeine$_{pre}$	123.751	115.056	132.447	113.938	0.889	562.000	77.555	0.248	
	Caffeine$_{post}$	114.685	101.733	127.636	109.000	0.889	546.222	79.456		<0.001
	Control	67.461	60.407	74.515	55.244	0.777	208.618	44.890		
E_L (cmH$_2$O/mL) / kg	Caffeine$_{pre}$	2.524	2.313	2.735	2.111	0.007	8.647	1.885	<0.001	
	Caffeine$_{post}$	0.935	0.894	0.977	0.968	0.100	1.677	0.253		0.138
	Control	1.008	0.923	1.093	0.915	0.001	2.365	0.541		
Z_L (cmH$_2$O/L/s) / kg	Caffeine$_{pre}$	335.811	311.809	359.813	280.479	1.719	895.347	214.075	<0.001	
	Caffeine$_{post}$	144.737	136.731	152.743	135.037	19.224	431.324	49.117		0.682
	Control	141.663	129.484	153.843	144.356	0.115	429.738	77.508		
W (gr•cm/s) / kg	Caffeine$_{pre}$	24.904	22.702	27.107	23.026	0.328	157.397	19.646	<0.001	
	Caffeine$_{post}$	69.926	59.858	79.994	55.948	1.261	302.664	61.762		<0.001
	Control	33.299	27.968	38.630	21.413	0.223	171.613	33.926		

breathe spontaneously for 1 min). The difference in W between Groups Caffeine$_{post}$ 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$_{post}$ - 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$_{post}$ and Control were performed on a comparable sample size on a per patient and overall basis. All study subjects were chosen within a very narrow PCA range. Also, the Group Caffeine responded clinically to caffeine by significantly reducing apneic periods. This increased the likelihood of finding

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a positive effect of caffeine. In terms of sample size calculations based on our primary finding i.e. V_T 7.3 ± 2.0 (Caffeine$_{post}$) vs 5.7 ± 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 work 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 V_E in the premature infant, there is a need to evaluate the efficacy of this drug in other groups of patients. So far, this drug has proven 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 V_E 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_E	Minute Ventilation
T_E	Expiratory Time
T_{TOT}	Total Breathing Time
T_I	Inspiratory Time
T_I/T_{TOT}	Time Cycle
W	Work of Breathing
PCA	Post-Conceptional Age
BPD	Bronchopulmonary Dysplasia
IVH	Intraventricular Hemorrhage
PaO_2	Partial Pressure of O2 in arterial blood
$PaCO_2$	Partial Pressure of CO2 in arterial blood
P_{ao}	Airway Opening Pressure
P_{es}	Esophageal Pressure
	Respiratory Flow
V	Respiratory Volume
FiO_2	Fraction of Inspired Oxygen
SaO_2	Oxygen Saturation
NICU	Neonatal Intensive Care Unit
R_L	Lung Resistance
E_L	Lung Elastance
P_{tp}	Transpulmonary Pressure = Pao - Pes
Z_L	Impedance
C_L	Dynamic Lung Compliance
C_{RS}	Dynamic Respiratory Compliance

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