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Effect of Caffeine on Oxygen Consumption and Metabolic Rate in Very Low Birth Weight Infants With Idiopathic Apnea

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ABSTRACT. *Objective.* Methylxanthines are among the most commonly prescribed drugs in neonatal intensive care. This study evaluates the effect of caffeine on oxygen consumption and metabolic rate in premature infants with idiopathic apnea.

Methods. Eighteen preterm infants at gestational ages from 28 to 33 weeks and birth weights of 890 to 1680 g were enrolled in the study. Nine preterm infants received caffeine therapy, and 9 served as a control group. Oxygen consumption and energy expenditure were examined before, during, and after caffeine treatment.

Results. Oxygen consumption increased significantly from 7.0 ± 0.9 before caffeine to 8.8 ± 0.7 mL/kg/min after 48 hours of caffeine therapy, and energy expenditure increased from 2.1 ± 0.3 to 3.0 ± 0.2 kcal/kg/hour. During the observation period of 4 weeks of caffeine treatment, oxygen consumption increased significantly in the caffeine group compared with the control patients. In the caffeine group, a lower environmental temperature was sufficient to maintain a normal body temperature. With similar caloric intake in both groups during the study period, daily weight gain in the control group was significantly higher (21 ± 4 vs 42 ± 2 g/d). None of the other parameters recorded changed during caffeine therapy.

Conclusion. Long-term administration of caffeine in preterm infants is associated with an increase in oxygen consumption and with a reduction of weight gain. This may have implications for clinical practice as nutritional regimens need to be adjusted during this therapy. *Pediatrics* 2001;107:660–663; *oxygen consumption, caffeine, apnea, preterm.*

ABBREVIATIONS. VLBW, very low birth weight; EE, energy expenditure; $\dot{V}O_2$, oxygen consumption; $\dot{V}CO_2$, carbon dioxide production.

Frequent and prolonged episodes of apnea are common in very low birth weight (VLBW) infants; the incidence and severity increase at lower gestational ages. A number of etiologic theories have been considered for central, obstructive, and mixed forms of apnea, although the pathogenesis is not understood clearly. Many preterm infants are treated with methylxanthines (caffeine, theophylline), which have been reported to stimulate

breathing efforts and have been used in clinical practice to reduce apnea since the early 1970s. Theophylline and caffeine are now among the most commonly prescribed drugs in neonatal intensive care.¹ The efficacy and therapeutic advantages of caffeine (1,3,7-trimethylxanthine) in preterm infants with idiopathic apnea have been evaluated and recommended by many groups.^{2–4} It is not known how the drug acts. A direct and generalized excitation of the central nervous system has been suggested and associated with an increased chemoreceptor responsiveness, based on increased breathing responses to CO_2 .⁵ Common side effects including tachycardia, agitation, and vomiting occur in 10% to 20% of infants who are treated with methylxanthines.^{3,6} Methylxanthines have been adopted as a common treatment for apnea of prematurity without evaluation of their long-term consequences and safety. The administration of methylxanthines in adults and experimental animals has been proposed as a means of promoting and maintaining weight loss by increasing energy expenditure (EE), because they have thermogenetic effects.^{7,8} Little is known about the long-term effects of caffeine on growth and metabolic rate in VLBW infants.

This study was designed to measure oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) by indirect calorimetry before, during, and after caffeine treatment in preterm infants, because any observed long-term changes in $\dot{V}O_2$ may influence the metabolic rate and reduce growth in VLBW infants. Changes in metabolic rate resulting from therapeutic doses of caffeine have not been measured in preterm infants before.

PATIENTS AND METHODS

Eighteen spontaneously breathing VLBW infants at gestational ages from 28 to 33 weeks (median: 30 weeks) were enrolled in the observation study. Nine infants received caffeine treatment for severe idiopathic apnea and were compared with a control group of 9 infants, matched for age and weight, with apnea but without caffeine therapy. In all infants, a first 45-minute series of indirect calorimetry ($\dot{V}O_2$ and $\dot{V}CO_2$) measurements was started in the first week of life and before caffeine treatment, and a second set of measurements was performed 48 hours after starting caffeine therapy. These tests were repeated under identical conditions every week, over a 4-week period. Finally, 6 days after stopping the caffeine therapy, indirect calorimetry was repeated.

Gestational age ranged from 28 to 33 weeks (median: 30 weeks) in the caffeine group and 29 to 34 weeks (median: 31 weeks) in the control group; birth weight ranged from 890 to 1680 g (median: 1230 g) and 890 to 1640 g (median: 1140 g), respectively. At the time of study, postnatal age ranged from 3 to 6 days (median: 4 days) in both groups. Apnea was defined as a breathing pause

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lasting longer than 20 seconds or a pause of <20 seconds associated with bradycardia (heart rate <100 beats per minute) and/or cyanosis. Apneic episodes were detected by continuous 24-hour cardiorespiratory monitoring. Causes of apnea other than prematurity had been ruled out, and all infants were clinically stable except for the apneic episodes. Indications for pharmacologic treatment were 3 or more apneic attacks occurring during a 1-hour period and requiring vigorous stimulation. The decision to prescribe caffeine for apnea was made by a neonatologist who was not participating in the study. Caffeine citrate was given intravenously in a single loading dose of 10 mg/kg and in subsequent doses of 5 mg/kg every 24 hours. Serum concentrations of caffeine ranged between 10 and 15 $\mu\text{g/ml}$. No other central or peripheral stimulating drugs were given during the entire study, and no infant received supplemental oxygen.

Both groups of patients received parenteral nutrition and bolus gavage feeding from the first day of life. Bolus enteral nutrition was augmented according to feeding tolerance. In the first study phase, all infants obtained 60% of their total daily fluid volumes as parenteral nutrition. Intravenous support was stopped in all study patients in the second weeks of life. In the beginning, all infants were fed either breast milk or a preterm formula every 2 hours. In the third study week, all infants received eight bolus feeds. During the study phases, total caloric and fluid intake was similar in both groups and body weights were measured daily. The rate of growth of each infant during caffeine treatment was determined from the change in body weight over the entire treatment period.

Room temperature ranged from 25°C to 29°C, and the humidity ranged from 35% to 45%. Indirect calorimetry was done in a double-walled, air temperature-controlled incubator (model 8000, Draeger AG, Lübeck, Germany) at thermoneutral temperature (ranging from 31°C-37°C) and at a humidity of 60% to 75% according to published recommendations.^{9,10} All of the infants were treated in the same type of incubator.

Behavioral states of infants were recorded throughout the observation period based on the modified Freymond Behavioral State Scale.¹¹ Four different behavioral states were distinguished: 0, eyes open or closed, regular respiration, no movements; 1, small movements; 2, vigorous movements; 3, crying. All of the infants were studied during sleep (state 0-1).

The infants were monitored continuously before, during, and after indirect calorimetry using a cardiorespiratory monitor (model VICOM-SMU; Marquette-Hellige GmbH, Freiburg, Germany) based on transthoracic impedance and with a pulse oximeter (Hellige or Nellcor Inc, Hayward, CA). Heart rate, respiratory rate, and oxygen saturation were monitored continuously, and periodic breathing, alarm, and event data (apneas, bradycardias, tachycardias, and oxygen saturation) also were recorded for 24 hours on a computer.

Skin (lower leg) and rectal temperatures were measured continuously 2 hours before, during, and 2 hours after indirect calorimetry (Exacon System 4000; Roskilde, Denmark). Room humidity and temperature were recorded during the observation periods.

Because oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) are influenced strongly by feeding, each period of indirect calorimetry began 45 minutes after each feeding and

lasted for 60 minutes.¹² The measurements were started after an equilibration time of 15 minutes, as recommended by the manufacturer. $\dot{V}O_2$ and $\dot{V}CO_2$ were measured by open-circuit continuous indirect calorimetry using a DELTATRAC II metabolic monitor (Datex-Ohmeda, Helsinki, Finland). This transportable device consists of a fast differential paramagnetic oxygen sensor and an infrared carbon dioxide sensor attached to a transparent hood that is ventilated continuously by a constant-flow generator, thus offering the advantage of ready access to the infant. We used the transparent hood for the preterm infants according to the criteria given by Bauer et al¹³ to prevent an increase in body temperature. This device does not measure inspiratory and expiratory oxygen concentration separately but measures 0.01% (vol) O_2 differences as a 1-minute average very accurately. Thus, at a Deltatrac flow constant of 3 L/min (room air and expiration air of the patient), the accuracy in $\dot{V}O_2$ measurements is ± 0.3 mL/min. Differential measurement is based on repeated automatic zeroing (every 4 minutes) during the measuring sequence. Calibration of the device was performed before each measurement by a standard calibration gas (5% CO_2 and 95% O_2). With room air, the analyzer was set at 0. Calibration gases were prepared to an accuracy of $\pm 0.03\%$ and certified gravimetrically. The DELTATRAC II stores each minute-to-minute value of $\dot{V}O_2$ and $\dot{V}CO_2$ electronically. We previously described the technique, precision, and accuracy of this oxygen consumption measuring device and its validation for indirect calorimetry in VLBW infants.¹⁴ At the end of the measurement, the values were transmitted to a personal computer and processed using SAS for Windows (SAS Institute, Cary, NC). EE was calculated as follows: $EE = 5.50 \dot{V}O_2 + 1.76 \dot{V}CO_2$ (in kilocalories per kilogram per hour).¹⁵

Mean values between the 2 study groups were compared using analysis of variance. *P* values below .05 were assumed to be significant. Correlation between the measured parameters was determined by regression analysis. Results are given as mean \pm standard error.

Informed consent was obtained from the parents of each infant studied.

RESULTS

Table 1 shows the major results before and after 2 days of caffeine treatment. Oxygen consumption increased significantly (*P* < .05) after 48 hours of caffeine therapy compared with pretreatment levels and with the control group. This rise in $\dot{V}O_2$ was accompanied by a significant increase in $\dot{V}CO_2$ and EE. The prevalence of apnea decreased from 20 ± 3 to 8 ± 5 episodes per day during caffeine treatment. During the study phases, the incubator temperature was lower in the caffeine treatment group (36.2 ± 0.4 vs $37.2 \pm 0.4^\circ\text{C}$) compared with the control group. Heart rate and respiratory rate were not significantly affected by caffeine.

The course of $\dot{V}O_2$ in the study population is

TABLE 1. $\dot{V}O_2$, $\dot{V}CO_2$, EE, and Physiologic Data Before and 48 Hours After Caffeine Treatment (Mean \pm Standard Deviation)

	Infants With Caffeine		Infants Without Caffeine	
	Before	During	Before	During
$\dot{V}O_2$ (mL/kg/min)	7.0 \pm 0.9	8.8 \pm 0.7*#	6.5 \pm 0.6	6.6 \pm 0.7
$\dot{V}CO_2$ (mL/kg/min)	6.6 \pm 0.7	8.5 \pm 1.0*#	6.1 \pm 0.8	6.6 \pm 0.5
EE (cal/kg/hr)	2.1 \pm 0.3	3.0 \pm 0.2*#	2.0 \pm 0.3	2.2 \pm 0.3
RR (min ⁻¹)	62 \pm 7	74 \pm 6	67 \pm 5	72 \pm 7
HR (min ⁻¹)	143 \pm 7	149 \pm 5	141 \pm 7	148 \pm 4
Sao ₂ (%)	95 \pm 3	96 \pm 4	96 \pm 4	95 \pm 3
Apnea/d	20 \pm 3	8 \pm 5*	12 \pm 4	11 \pm 3
Skin temperature (°C)	36.2 \pm 0.7	36.5 \pm 0.4	36.4 \pm 0.6	36.7 \pm 0.4
Rectal temperature (°C)	37.3 \pm 0.6	37.2 \pm 0.5	37.4 \pm 0.7	37.3 \pm 0.3
Incubator temperature (°C)	37.5 \pm 0.4	36.2 \pm 0.4*	37.4 \pm 0.4	37.2 \pm 0.4

RR indicates respiratory rate; HR, heart rate; Sao₂, oxygen saturation.

* *P* < .05 compared with baseline values; # *P* < .05 compared with control group.

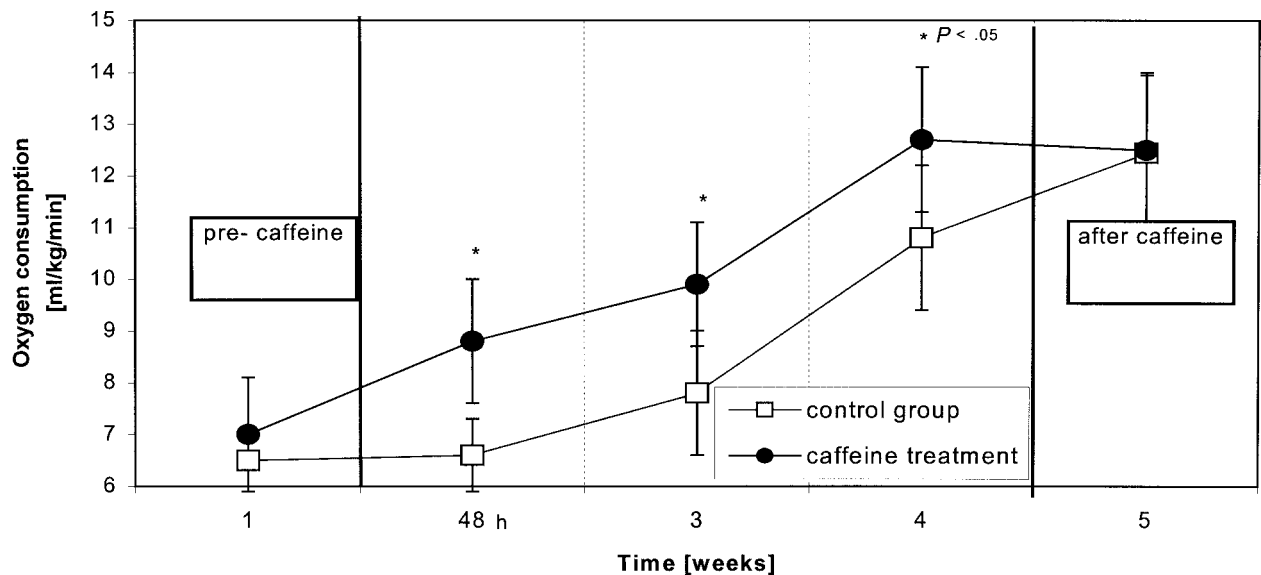


Fig 1. Oxygen consumption before, during, and after caffeine treatment in preterm infants.

shown in Fig 1 and Table 1. In both groups, the mean levels of $\dot{V}O_2$ increased with postnatal age. $\dot{V}O_2$ began to rise 48 hours after the first caffeine dose and remained above the control levels during the 4 weeks of treatment ($P < .05$).

The mean caloric intake was similar in both groups. Caloric intake was increased during the study period from 87 ± 9 to 123 ± 7 kcal/kg/d in the caffeine group and from 86 ± 10 to 124 ± 8 kcal/kg/d in the control group. Parenteral nutrition was stopped in both groups at the same time. No gastrointestinal complications were observed.

The weight gain during the 4 weeks of treatment was 220 g in the caffeine group and 433 g in the control group. The mean daily weight gain during the study period averaged 12 ± 2 g/d in the caffeine group and 21 ± 4 g/d in the control group ($P < .01$).

DISCUSSION

The present study is the first to show oxygen consumption before, during, and after long-term caffeine administration in premature infants. In accordance with previous trials, our results reveal that caffeine therapy reduces frequency and duration of idiopathic apnea in premature infants.^{2,3} During the past 25 years, methylxanthines have been used extensively in the treatment of apnea in prematurity without an evaluation of its long-term safety. Bio-transformation of theophylline is different in the preterm infant compared with adults.¹⁶ In contrast to adults, theophylline is metabolized into the active metabolite caffeine in preterm infants.⁶ Caffeine has potential therapeutic advantages over theophylline and is less likely to cause side effects in the central nervous system or gastrointestinal tract.^{16,17} Furthermore, plasma levels of caffeine tend to be more stable compared with theophylline.¹⁶ The precise mechanisms of action, potential long-term toxicity, and late effects of prolonged administration of caffeine on oxygen consumption and metabolic rate in premature infants are not well known.

Oxygen consumption and EE increased with age in both groups during the study period (Fig 1). The rise in metabolic rate with advancing postnatal age has been explained by increases in energy intake and weight gain.¹⁸ Factors that are known to influence the metabolic rate in the neonate include illness, activity, composition of food, and thermal environment.¹⁹ In our study, both groups had similar energy intake and gestational and postnatal ages, thereby minimizing influences of other factors that affect the $\dot{V}O_2$ measurements. Patients were not randomized to receive caffeine therapy for ethical reasons. The infants of the control group were matched for gestational age and birth weight but had fewer apneic events. All infants were studied in a stable state, and activity states in the 2 groups were comparable during calorimetry. It is unlikely that the different frequencies of apneic events in the 2 groups influenced the results, because $\dot{V}O_2$, $\dot{V}CO_2$, and EE were similar in the 2 groups before caffeine was started and after caffeine was stopped in the treatment group (Table 1, Fig 1).

We found in the treatment group during the first 48 hours a marked increase of $\dot{V}O_2$, $\dot{V}CO_2$, and EE (Table 1) that persisted until the end of caffeine treatment. Different hypotheses have been proposed for the increase in $\dot{V}O_2$ during treatment with methylxanthines. Gerhardt et al²⁰ found an increase in metabolism in premature infants during aminophylline therapy by means of indirect calorimetry. In contrast, Fjeld et al,²¹ using double-labeled water, reported no apparent effects of therapeutic doses of theophylline on EE in preterm infants with apnea. This discrepancy may be attributed to the different methods. The double-labeled method does not seem to be accurate in the preterm infant, because the state of hydration changes substantially in the postnatal period.^{22,23} Calorimetry in premature infants showed that aminophylline increased $\dot{V}O_2$ by 20% and that was accompanied by increases in minute ventilation and in the central responsiveness to carbon dioxide.²⁰ Stud-

ies in adult rats have also shown a sustained rise in metabolic rate by ~20% with aminophylline that was associated with an increase in physical activity.²⁴ Our infants were studied under resting conditions, so it is unlikely that increased physical activity contributed to the increased oxygen consumption during caffeine therapy. In adults, theophylline has been shown to induce changes in sleep state. Milsap et al²⁵ reported an increase in $\dot{V}O_2$ associated with changes in sleep states in premature infants who were treated with theophylline. The heart rate may increase markedly in response to theophylline,²⁶ whereas no significant change in heart rate was observed with caffeine (Table 1). This may be explained by more pronounced sensitivity of the phosphodiesterase in cardiac muscle during theophylline treatment when compared with caffeine.^{27,28} High doses of caffeine may increase respiratory rate and lead to generalized central nervous system excitation.²⁹

In our study, no significant changes in skin or rectal temperatures were noted during theophylline treatment (Table 1). However, in the caffeine group, a lower environmental temperature was required to maintain normal skin and rectal temperatures (Table 1). Less demand of heat input has also been observed in premature infants who are treated with aminophylline.²⁰ Increased heat production may explain the thermal effects of methylxanthines in infants. Proper adjustment of the environmental temperature probably prevented rises in skin and rectal temperatures and possibly also contributed to the maintenance of heart and respiratory rate.

The rise in oxygen consumption and EE may have contributed to the smaller weight gain in the caffeine-treated preterm infants. The negative effect of caffeine on body weight has been used successfully in obese people and animals.^{7,30,31} Caffeine has been shown to decrease lipid accretion, accelerate muscle protein deposition, promote thermogenesis, and increase oxygen consumption and metabolic rate.³¹

CONCLUSION

Caffeine treatment in VLBW infants is associated with long-term metabolic stimulation that exceeds normal maturational changes. This may have implications for clinical practice as feeding or environmental temperature need to be adjusted during this therapy. These results have to be confirmed in a larger population before high-calorie supplemental feeding is considered for premature infants during treatment with methylxanthines.

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