Effect of caffeine on peripheral chemoreceptor activity in premature neonates: interaction with sleep stages

Karen Chardon, Véronique Bach, Frédéric Telliez, Virginie Cardot, Pierre Tourneux, André Leke, and Jean-Pierre Libert

Effect of caffeine on peripheral chemoreceptor activity in premature neonates: interaction with sleep stages. J Appl Physiol 96: 2161–2166, 2004. First published February 13, 2004; 10.1152/japplphysiol.01160.2003.—Caffeine is widely used for the treatment of apnea in premature neonates. However, the localization of caffeine’s target site (central nervous system and/or peripheral chemoreceptors) is not well defined, especially for sleeping neonates whose sleep stages interact with respiratory control. The aim of this study was to assess the activity of the peripheral chemoreceptors in relation to sleep stages in premature neonates treated (or not) with caffeine for idiopathic apnea. Peripheral chemoreceptor activity was assessed in 22 neonates (postconceptional age of 36 ± 1 wk with birth weights ranging from 790 to 1,910 g) by performing a 30-s hyperoxic test during active and quiet sleep. Eleven neonates received caffeine treatment (4.0 ± 0.5 mg·kg⁻¹·day⁻¹) and 11 served as controls. For all neonates, the decrease in minute ventilation observed during hyperoxia was greater during active than during quiet sleep. Neonates receiving caffeine showed a significantly greater decrease in ventilation during hyperoxia in both sleep stages, compared with controls (caffeine; −29.7 ± 12.8% vs. control; −22.0 ± 7.4%; F₁₁₅ = 4.6, P = 0.04). We conclude that caffeine administration increases the effectiveness of chemoreceptor activity. Because sleep stage durations were not affected by the treatment, it is likely that the decrease in apneic episodes typically observed with caffeine therapy is only related to respiratory processes and is independent of the sleep stage organization.

APNEA IS THE MOST FREQUENT disorder of breathing control in premature neonates, and neonatal care units habitually use methylxanthine derivatives (such as caffeine) to treat these events (3). It has been reported that caffeine increases breathing frequency, decreases the number of apneic spells, and reduces Paco₂ and the need for (and duration of) mechanical ventilation in premature infants with apnea (2). Because peripheral chemoreceptors provide feedforward control of respiration, which can thus terminate apnea and initiate normal breathing (17, 31), it could be supposed that these receptors are an important target for caffeine action in premature neonates. Peripheral chemoreceptor activity is typically assessed by monitoring the rapid decline in minute ventilation (Ve) (in the first minute) after inhalation of pure O2 (16). This drop in ventilation involves an acute reduction in peripheral chemoreceptor inputs (i.e., physiological chemodenervation) and thus reflects the strength of the peripheral chemoreceptor drive. The decrease is ultimately followed by an increase in ventilation that is centrally mediated. Although the respirogenic properties of the methylxanthine family (and especially caffeine) are well documented, little is known about the localization of caffeine’s target site and its mechanism(s) of action; it is generally assumed that the drug induces direct and widespread stimulation of central nervous structures, thus increasing supra pontine respiratory drive. The stimulating action of caffeine has been related to its direct excitatory effect on the neurons controlling ventilation. This is supported by several studies performed in animals after extirpation of the carotid sinus nerves and vagal section (27, 32). Experiments carried out with a CO2 stimulus also confirm this hypothesis, because the ventilatory response to CO2 (which mainly depends on central receptors) is increased by caffeine administration (20). This could be explained by a downward shift of the threshold for CO2 responsiveness in the respiratory center. However, this action may not be completely central, because increased ventilation is not found in the absence of intact carotid body receptors in lambs (6), and aminophylline failed to reverse hypoxic depression after carotid body denervation in newborn piglets (11). Thus the question of an increase in peripheral chemoreceptor responsiveness (associated or not with a direct, central action of caffeine) remains debatable, particularly in human neonates because all the above studies were performed in animal models for which chemodenervation can alter respiratory behavior and can lead to sudden death (19). To our knowledge, only one study has dealt with sleeping neonates (12): it showed that hyperoxia induces a greater decrease in ventilation after ingestion of aminophylline (10 mg/kg). This study was performed in infants who did not suffer from ventilatory problems and so each infant served as his or her own control, i.e., before and after administration of aminophylline. The apnea frequency and the different sleep stages were not scored.

There is still a great deal of debate surrounding the action of methylxanthines on sleep organization in general and on active sleep (AS) in particular, because apneic events are more frequent during the latter. In premature infants, Thomann et al. (34) reported that theophylline decreases AS, whereas Dietrich et al. (18) found the opposite effect. More recently, Curzi-

Address for reprint requests and other correspondence: K. Chardon, Laboratoire ETP-APC (EA2088), Faculté de Médecine, Université de Picardie Jules Verne, 3 rue des Louvels, F-80036 Amiens cedex, France (E-mail: karen.chardon@su.u-picardie.fr).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
of caffeine of 11.5
morning dose regimen was chosen to achieve plasma concentrations
fine neonates who had shown more than one signi-
hour during the
fall of heart rate below 100 beats/min or a fall in blood O2 level of at
oral caffeine citrate treatment (4.0
had given their written consent. The protocol was approved by the
were enrolled after the parents had been informed of the protocol and
from the study.

Dascalova et al. (13) showed that caffeine did not modify the
duration of AS, and a similar finding has been reported by
Gabriel et al. (24) with aminophylline. The decrease in apneic episodes
during methylxanthine therapy can thus be explained by an action on the respiratory controller and/or by sleep stage
disturbances. Indeed, a previous study has shown that a
decrease in AS duration lowered the frequency of apneic events (23).

The aim of the present study was 1) to assess whether
caffeine treatment in premature neonates stimulates ventilation
through peripheral chemoreceptors and 2) to determine the
potential influence of sleep states. The mechanism of caffeine’s
action on the peripheral chemoreflex was assessed by moni-
toring immediate changes in the respiratory pattern in response
to a 30-s hyperoxic test (HT) performed during AS or quiet
sleep (QS).

MATERIALS AND METHODS

Subjects. Twenty-two premature neonates (gestational age: 31 ± 2
wk, postconceptional age: 36 ± 1 wk, birth weight: 1,457 ± 304 g)
were enrolled after the parents had been informed of the protocol and
had given their written consent. The protocol was approved by the
Picardy Regional Ethics Committee.

The caffeine group (Table 1) consisted of 11 neonates receiving an
oral caffeine citrate treatment (4.0 ± 0.5 mg·kg⁻¹·day⁻¹) for idio-
pathic apnea as recommended by Hascoët and Boutroy (30). This
morning dose regimen was chosen to achieve plasma concentrations
of caffeine of 11.5 ± 2.4 mg/l. The treatment was delivered to
neonates who had shown more than one significant apneic episode
per hour during the first hours of life. A significant apneic episode
was defined as a respiratory arrest of 7 s or more, associated with either a
fall of heart rate below 100 beats/min or a fall in blood O2 level of at
least 10% relative to the previous baseline. The decision to treat was
made by medical staff other than those involved in the study. After 3
wk of treatment, the neonates were compared with a control group (11
neonates not undergoing caffeine therapy) matched for age and body
mass. Neonates with neurological or cardiac disorders were excluded from the study.

Table 1. Clinical parameters for the 2 groups of neonates

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Caffeine</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>31.1 ± 1.8</td>
<td>30.3 ± 2.0</td>
<td>0.33</td>
</tr>
<tr>
<td>Postnatal age, days</td>
<td>34 ± 14</td>
<td>36 ± 17</td>
<td>0.83</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>1,443±347</td>
<td>1,470±272</td>
<td>0.84</td>
</tr>
<tr>
<td>Postconceptional age, wk</td>
<td>36.1±0.8</td>
<td>35.4±1.2</td>
<td>0.18</td>
</tr>
<tr>
<td>Body mass, g</td>
<td>2,076±139</td>
<td>2,112±137</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Values are means ± SD. Between-group differences tested by analysis of variance were not significant (p values).

The temperature of the air circulating inside the incubator was measured with a thermocouple (accuracy ± 0.10°C after calibration, thermocouple K; Bioblock, Illkirch, France) located 10 cm above the head of the neonate. Mean skin temperature (°C) was calculated from the average of two skin temperatures measured by thermocouples attached to the right-hand side of the abdomen (°C) and on the right cheek (°C). Each probe was covered by an aluminum foil patch to reduce the effect of heat radiation from the incubator walls. Rectal temperature (°C) was monitored with a thermistor probe (accuracy ± 0.10°C after calibration, YSI 402, Bioblock) inserted 3 cm beyond the anal sphincter. Body and air temperatures were continuously sampled at 10-s intervals and were averaged across the whole experiment, i.e., during interfeeding intervals (2–3 h) (33).

Sleep stages [AS, intermediate sleep (IS), and QS] were scored online in 30-s periods (15), on the basis of the following recordings: two electroencephalograms from the right and the left rolando-occip-
tal leads; eye movements monitored by a piezo-electric quartz trans-
ducer attached to the eyelid; body movements monitored by actime-
ters attached to the wrist and ankle, together with visual observations
noted on the recording. The different sleep stages are expressed as percentages of total sleep time (TST). Breathing movements were measured by thoracic impedanciometry.

Electrocardiograms were recorded using self-adhesive electrodes and standard derivations, and O2 saturation was monitored throughout the experiment using a pulse oximeter with a neonatal sensor.

The HT (9) consisted of a 30-s normoxic baseline period during
which the neonate breathed air from the incubator, then a 30-s
hyperoxic period with 100% O2 inspired from a bag and expired into
the incubator, and finally a 30-s recovery period with air from the
incubator. To perform the test, a face mask attached to a pneumota-

graph (Statice Santé, Besançon, France) was placed over the
neonate’s face (total instrumental dead space: 2.5 ml) gently and
consistently by the same experimenter. Care was taken to avoid
leakage. The flow signal was converted into an analog signal via a
pressure transducer (Validyne DP 45-16, ±2 cmH2O) driven by an
amplifier (Gould), as previously described and validated in various
studies (8, 9). A two-way electric valve (response time: 10 ms)
attached to the pneumotachograph was controlled by a computer
program so as to produce 30-s square waves of 100% inspired O2.
Depending on the flow direction, the two-way valve gave access either
to a bag containing 100% O2 (inspiratory channel during the HT) or
to incubator air (expiratory channel during the HT). At the end of the

Table 2. Mean temperatures of air incubator and neonates

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Caffeine</th>
<th>Between-Group Comparison</th>
<th>Caffeine × Sleep Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teq</td>
<td>32.3±0.6</td>
<td>32.0±0.5</td>
<td>F1,15 = 2.00</td>
<td>p = 0.18</td>
</tr>
<tr>
<td>Trec</td>
<td>37.1±0.2</td>
<td>37.1±0.4</td>
<td>F1,15 = 0.03</td>
<td>p = 0.86</td>
</tr>
<tr>
<td>Ta</td>
<td>36.3±0.2</td>
<td>36.3±0.3</td>
<td>F1,15 = 0.003</td>
<td>p = 0.96</td>
</tr>
<tr>
<td>Tcheek</td>
<td>35.8±0.3</td>
<td>35.8±0.4</td>
<td>F1,15 = 0.02</td>
<td>p = 0.90</td>
</tr>
<tr>
<td>Tabdo</td>
<td>36.8±0.2</td>
<td>36.8±0.3</td>
<td>F1,15 = 0.02</td>
<td>p = 0.93</td>
</tr>
</tbody>
</table>

Values are means ± 1 SD in °C. Teq, incubator thermal equilibrium; Trec, rectal temperature; Tam, mean skin temperature; Tcheek, cheek skin temperature; Tabdo, abdominal skin temperature. Between-group differences and potential interactions between caffeine and sleep were tested by analysis of variance (F and p values are given).
30-s baseline period, the computer detected the last normoxic expiration to switch the valve when the flow signal changed (i.e., at the inspiration-expiration transition) and then started the hyperoxic period. The next inspiration was 100% O₂ from the bag. At the end of the inspiration, the electric valve switched to the other channel and the neonate expired into the incubator, and so on throughout the 30-s hyperoxic period. Although this type of setup tends to increase \( \dot{V}E \) and tidal volume (\( V_{T,1} \)), both effects are transient. Nevertheless, at least 1 min elapsed before data storage onset to ensure that no change occurred in the respiratory pattern and state of alertness. One test was performed during AS and QS for each neonate because ventilatory response reproducibility of HT has been assessed elsewhere (9).

Central apneas (longer than 3 s) were counted and related to sleep stages (14). For technical reasons, respiratory frequency (\( f \)) was only recorded for 20 neonates. Apnea frequencies (apneas/h) and mean and maximal durations (s) were analyzed. Sleep and apneas were scored during the interfeding intervals of about 3 h on average, during which HTs were not performed to reduce the potential influence of the procedure on sleep and respiratory events. If no apnea occurred during this period, the apnea frequency was 0 apneas/h whereas the mean and maximal durations were considered as missing values in the statistical analysis.

Respiratory flow was integrated for breath-by-breath measurements of \( \dot{V}E \) (ml·min\(^{-1}\)·kg\(^{-1}\)), \( V_{T,1} \) (ml), inspiratory time (\( T_i \), s), expiratory time (\( T_e \), s), total respiratory cycle duration (\( T_{tot} \), s), \( f \) (breaths/min), duty cycle (\( V_{T,1}/T_{tot} \)), and mean inspiratory flow (\( V_{T,1}/T_{tot} \), ml·min\(^{-1}\)·kg\(^{-1}\)). O₂ and CO₂ fractions were measured breath by breath via a mass spectrometer (MGA 1100, Perkin-Elmer, Pomona, CA).

The response time (RT, s) to the HT was defined as the time elapsing from the hyperoxia onset to the first statistically significant change in ventilation (\( \dot{V}E \) (one-way ANOVA, based on a moving window average of four breaths compared with the baseline period)) as recommended by Bouferrache et al. (9). The percent change at RT was assessed for all respiratory parameters reported above. Various test durations have been undertaken in the literature, ranging from one or two breaths to >1 min. There is no evidence, however, that peripheral chemoreceptor inputs are cancelled out when the duration is limited to one or two breaths. On the other hand, for longer durations, the ventilatory decrease was typically averaged. This procedure therefore underestimates the strength of peripheral chemodenervation (also the early phase of the subsequent increase in ventilation, which is more related to central processes. To avoid these problems, we used a standardized and validated method to perform the test and analyze the respiratory variables (8, 9).

**Statistical analysis.** Thermal, sleep and apneic parameters were analyzed by one-way ANOVA for repeated measures with caffeine treatment as a between-subject factor, i.e., the caffeine group vs. the control group. These analyses were performed on the ventilatory parameter values averaged over the 30-s normoxic period and on the respiratory variables measured for the HT response time. Degrees of freedom were corrected using the Geisser and Greenhouse method (28). Main effects were caffeine treatment and sleep stage, and interactions between these effects were also tested. When the condition effect or interactions were significant, post hoc t-tests were carried out.

Values expressed as percentages were arcsine transformed to stabilize the variance (35). \( F \) values are given in the text with the corresponding degrees of freedom and probabilities. A \( P < 0.05 \) was set as the significance level. Indicative results (0.05 < \( P \) < 0.10) are sometimes given in the text below, when relevant. Data are given as means ± SD.

**RESULTS**

At thermal equilibrium (Table 2), the incubator air temperature did not differ significantly between the two groups of neonates. For body temperatures, no significant effect of caffeine or caffeine × sleep state interactions was found.

As regards the sleep parameters (Table 3), there was no effect of caffeine either on the TST or on the sleep stage durations expressed as percentages of TST.

No significant group effects on the apnea frequency and mean or maximum durations (Table 4) were found. In both groups, a sleep state effect on frequency and maximal duration was found: it was significantly greater (\( P < 0.001 \)) during AS than during QS (frequency: 47.9 ± 27.4 vs. 18.6 ± 17.0 apneas/h, respectively; maximal duration: 10.0 ± 2.2 vs. 6.5 ± 3.8 s, respectively). The treatment did not modify the relationship between apneas and sleep stages, because the interaction between these events was not significant (\( F_{1,14} = 0.12; P = 0.73; F_{1,14} = 0.34; P = 0.57 \) for the apnea frequency and maximum duration).

The mean \( \text{SaO}_2 \) was 97 ± 2% at baseline and remained at 100% during the hyperoxic period. The mean heart rate was 142 ± 6 beats/min before the hyperoxic period. No significant caffeine or sleep state effects were observed for these two parameters.

A significant sleep state effect was observed for all respiratory parameters, with the exception of \( V_{T,1} \) (Table 5). As expected, \( \dot{V}E \) and the mean inspiratory flow (\( V_{T,1}/T_{tot} \)) were lower during QS than in AS. The decrease in \( \dot{V}E \) was mainly explained by the drop in \( f \) that occurred during QS.

When all sleep stages were pooled, the caffeine group tended to have higher (although not statistically significant) \( \dot{V}E \) values compared with the baseline period (0.05 < \( P < 0.10 \)).

---

**Table 3. Sleep parameters in the 2 groups of neonates**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Caffeine</th>
<th>Treatment Effect (( F; P ) values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST, min</td>
<td>120 ± 22</td>
<td>111 ± 20</td>
<td>( F_{1,15} = 0.72; P = 0.41 )</td>
</tr>
<tr>
<td>AS, %TST</td>
<td>67 ± 9</td>
<td>70 ± 10</td>
<td>( F_{1,15} = 0.57; P = 0.58 )</td>
</tr>
<tr>
<td>IS, %TST</td>
<td>11 ± 6</td>
<td>7 ± 6</td>
<td>( F_{1,15} = 1.43; P = 0.17 )</td>
</tr>
<tr>
<td>QS, %TST</td>
<td>24 ± 7</td>
<td>21 ± 10</td>
<td>( F_{1,15} = 0.72; P = 0.48 )</td>
</tr>
</tbody>
</table>

Values are means ± SD. TST, total sleep time; AS, active sleep; IS, indeterminate sleep; QS, quiet sleep. \( F \) and \( P \) values are given for the between-group differences.

---

**Table 4. Apnea frequency and mean and maximal durations between sleep state in the 2 groups of neonates**

<table>
<thead>
<tr>
<th></th>
<th>Control AS</th>
<th>Control QS</th>
<th>Caffeine AS</th>
<th>Caffeine QS</th>
<th>Treatment Effect (( F; P ) values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency, apneas/h</td>
<td>46.4 ± 22.3</td>
<td>23.8 ± 18.4</td>
<td>49.0 ± 36.0</td>
<td>16.9 ± 15.12</td>
<td>( F_{1,14} = 0.41; NS )</td>
</tr>
<tr>
<td>Mean duration, s</td>
<td>6.1 ± 1.7</td>
<td>5.6 ± 0.8</td>
<td>4.9 ± 0.4</td>
<td>4.9 ± 2.1</td>
<td>( F_{1,14} = 0.50; NS )</td>
</tr>
<tr>
<td>Maximal duration, s</td>
<td>10.6 ± 2.5</td>
<td>8.2 ± 3.0</td>
<td>9.2 ± 1.3</td>
<td>6.2 ± 1.7</td>
<td>( F_{1,14} = 2.9; NS ); ( F_{1,14} = 26.1; P &lt; 0.001 )</td>
</tr>
</tbody>
</table>

Values are means ± SD. NS, not significant. \( F \) and \( P \) values are given for the between-group differences and sleep state effects.

---

**J Appl Physiol • VOL. 96 • JUNE 2004 • www.jap.org**
(F = 0.08), whereas Vt/Ti increased significantly. There were no caffeine × sleep state interactions for baseline ventilatory parameters.

The RT elapsing between the hyperoxia onset and the first significant change in V̇E was not affected by the caffeine treatment (9.5 ± 3.9 vs. 10.7 ± 4.8 s for control and caffeine groups, respectively; F_{1,15} = 0.73) or by the sleep states (F_{1,15} = 0.64).

Figure 1 shows the decline in ventilatory parameters measured at RT in response to the HT, in AS and QS and for the two groups of neonates. V̇E decrease was the only respiratory parameter that was significantly modified by the sleep stage: the drop was higher during AS than during QS (−30.6 ± 11.1% vs. −20.7 ± 8.2%, F_{1,15} = 16.3, P = 0.001 for the neonates as a whole).

The drop in V̇E was enhanced in the caffeine group (control group: −22.0 ± 7.4% vs. caffeine group: −29.7 ± 12.8%; F_{1,15} = 4.6, P = 0.04), whereas the changes in Vt, f, and Vt/Ti were similar in the two groups. No caffeine × sleep state interaction was found for these responses to inhalation of pure O_2.

**DISCUSSION**

The incubator air and body temperatures did not differ significantly between the two groups of neonates. Moreover, our results show that there was no significant difference in sleep structure between the controls and the caffeine-treated neonates. In contrast to previous studies, we found neither an increase (18) nor a decrease (34) in the mean duration of AS with caffeine treatment. The present findings confirm those of Gabriel et al. (24) and of Curzi-Dascalova et al. (13), who reported that sleep organization was not disturbed in premature infants treated with low doses (5 mg·kg⁻¹·day⁻¹) of oral caffeine citrate.

Although the two groups were comparable in age and weight, they may have differed with respect to their respiratory control. However, Fagenholz et al.’s (21) study of resting ventilation and the ventilatory response to 100% O_2 and to CO_2 test (5% CO_2) pointed out that there was no significant difference in chemoreceptor function (peripheral and central chemoreceptor activity) between normal infants and those suffering from prolonged apnea. These authors also demonstrated that there was no significant difference in ventilatory response to CO_2 or 100% O_2 for each sleep stage when controls and affected infants were compared. Thus, in the present study, it can be held that respiratory status, at least in terms of chemoreceptor control, was the same in the two groups of neonates.

**Table 5. Sleep state and caffeine effects on ventilatory parameters during the normoxic period**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Caffeine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AS</td>
<td>QS</td>
</tr>
<tr>
<td>V̇E (ml/min/kg)</td>
<td>371±99</td>
<td>290±77</td>
</tr>
<tr>
<td>Vt (ml/kg)</td>
<td>6.7±1.9</td>
<td>6.5±1.5</td>
</tr>
<tr>
<td>f (breaths/min)</td>
<td>57.0±10.6</td>
<td>45.3±7.5</td>
</tr>
<tr>
<td>Vt/Ti (ml/kg)</td>
<td>895±223</td>
<td>776±185</td>
</tr>
</tbody>
</table>

Values are mean ± SD. V̇E, minute ventilation (ml/min); Vt, tidal volume (ml/kg); f, respiratory frequency (breaths/min); Vt/Ti, mean inspiratory flow (ml/min·kg⁻¹). F and P values are given.
Sleep states and ventilation. Sleep states influence the ventilatory parameters recorded during normoxia. As expected, the f was higher during AS than during QS for the two groups of neonates, confirming the well-known interaction between sleep states and the respiratory pattern (25). As a result, the magnitude of V̇E was greater during AS than during QS.

An interaction between the sleep states and ventilatory processes was also found during the HT: the fall in V̇E was larger during AS than during QS, suggesting that the peripheral chemoreceptors activity was more intense during AS.

Multiple neural sites might mediate this interaction. Afferent inputs from the carotid sinus chemoreceptors to the nucleus of the solitary tract project to the ventral medullary surface (VMS) (10). Thus the nucleus of the solitary tract exerts disfacilitory influences on intermediate VMS area neurons. The sensitivity of the rostral and intermediate VMS areas to a breathing challenge could be modified by the sleep state, because it has been shown in animals that the neural activity in this region decreases during rapid eye movement sleep (29). Afferent projections to this region could mediate respiratory and sleep interactions, although this remains a matter of debate.

Caffeine effect. As shown by the results reported in Table 4, caffeine therapy brought down the duration and the frequency of idiopathic apneas to levels comparable to those observed in premature neonates not requiring treatment. Moreover, it is clear that the treatment is effective during AS as well as during QS. Apnea frequencies and maximal durations are greater during AS than during QS, with or without caffeine therapy. Because the durations of these sleep stages are unaffected by the treatment, it is evident that the decrease in apneic episodes induced by caffeine administration is independent of sleep stage disturbances. Our results show that when the peripheral chemoreceptors operated under normoxic conditions, the caffeine group exhibited increased respiratory drive (mean inspiratory flow V̇r/Tl), whereas the time index (f) was unchanged. This finding confirms that of Aranda and Turmen (3), who pointed out that caffeine exerts its “antiapneic” effects by increasing the respiratory center output, as evidenced by increased V̇r/Tl.

During the HT (and regardless of the sleep stage), the ventilatory decrease persists in the caffeine group and is greater than in the controls. Our data strongly suggest that the effectiveness of chemoreceptor activity is enhanced during caffeine administration, because the drug amplifies the drop in ventilation compared with controls. This agrees with the findings of Cattarossi et al. (12), who showed in a longitudinal study that aminophylline augmented the ventilatory decrease induced by hyperoxia in newborn infants, ascribing an enhancement of peripheral chemoreceptors activity with the drug. Similarly, Blanchard et al. (6) showed in lambs that peripheral chemoreceptors are crucial for caffeine action, because chemodenervation completely abolished the ventilatory response to the drug. The data reported above and those of the present study clearly indicate that the peripheral chemoreceptors’ contribution is crucial. Unfortunately, the mechanism of action by which caffeine acts on chemoreceptor activity is unknown.

However, in the present study we cannot rule out a direct effect of caffeine increasing the responsiveness of the central nervous structures that control ventilation. The present conclusion applies to the early transitional response to the test and may well not hold for the subsequent increase in V̇E, which probably requires a combined effect of central and peripheral receptors. This has been demonstrated with higher than usual caffeine dosages that produce centrally mediated ventilatory stimulation in conscious cats (27). These authors showed that hyperventilation was observed in carotid body denervated cats given 30 mg·kg⁻¹·h⁻¹ caffeine.

The major contribution of the peripheral chemoreceptors found in the present study could explain the fact that the apneas are more frequent in preterm than in full-term neonates (26), because the chemoreceptors mature during the transition from fetal to postnatal life. This remains controversial, because one study has reported more active peripheral chemoreceptors in preterm than in full-term infants (1). Similarly, the transient effect of caffeine in kittens shows similar ventilatory response patterns to those seen in adult cats (5).

Furthermore, the higher chemoreceptor activity in the caffeine group might alter the infants’ responsiveness to a chemical stimulus. For example, babies exposed to a hypoxic challenge (for example in a rebreathing situation) might be unable to increase their ventilation, which would ultimately lead to death. Therefore, caffeine treatment may represent an additional sudden infant death syndrome risk factor (7).

In conclusion, the present study demonstrates that peripheral chemoreceptor activity is increased by caffeine in premature neonates during AS and QS. However, it is not possible to discard that the increase of effectiveness of chemoreceptor may also reflect a change in the central processes. The antiapneic effect of caffeine is not related to sleep state disturbances but rather to a direct action on processes controlling respiration.

ACKNOWLEDGMENTS

We thank Stephane Delanaud and the staff of the Department of Pediatrics at the University Hospital Center Nord Amiens for experimental collaboration. Our warm gratitude goes to the neonates who participated in this study and their parents. We thank David Fraser for English corrections.

GRANTS

This work was supported by the Regional Council of Picardy and the French Ministry of Research. V. Cardot was granted by the Regional Council of Picardy and the European Social Fund.

REFERENCES


