

J. Perinat. Med.
6 (1978) 280

Sleep state and arterial blood gases and pH, in human newborn and young infants

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1 Introduction

Sleep state influences the respiratory pattern in adults and infants. Most normal infants between 35 and 46 weeks post-conceptual age have 2 distinct sleep states: Quiet and active. These are analogous to the non-rapid eye movement (NREM) and rapid eye movement (REM) sleep of older subjects. Active sleep is associated with greater respiratory frequency, minute ventilation [3, 8, 11, 12] oxygen consumption [18] and frequency of respiratory pauses [3, 5, 6, 7, 10, 20] and with a more irregular respiratory pattern than quiet sleep. ASERINSKY [2] has shown that in adults there is an association between REM and fall in arterial oxygen saturation. If this occurred in prematurely born infants it might depress the respiratory center and lead to long periods of apnea and increasing respiratory irregularity [16].

The purpose of this study was to determine whether there was arterial hypoxemia or hypercarbia associated with active sleep in infants with mild chronic lung disease.

2 Method

All of the twelve study subjects were to have an arterial blood sample for their clinical management, and none required an oxygen-enriched environment at the time of study. The pertinent clinical data are shown in Tab. I.

Curriculum vitae

Dr. JOHN G. BROOKS was born in Cambridge, Massachusetts, in 1942. He received his M.D. degree from Harvard University and his pediatric training at the University of Colorado. He took a fellowship in pediatric pulmonary physiology and disease at the Cardiovascular Research Institute, University of California. He is currently Assistant Professor of Pediatrics and Co-director of the Pediatric Pulmonary Service at the University of Colorado. His research interest is the development of the control of breathing.



We studied the infants in a quiet, partially darkened room in the intensive care nursery between 11 a.m. and 4 p.m., beginning 1–2 hours after a regular feeding, and maintained rectal temperature, measured continuously, between 36–37° C by a servo-controlled overhead radiant heater. After cannulating a branch of the superficial temporal artery by our standard method [17], we filled the indwelling needle with a solution containing 20 U heparin/ml normal saline and were able to obtain samples without altering the infants sleep state. We then placed silver-silver chloride or gold plated, disc type electrodes on each of the frontal, parietal,

Tab. I. Clinical data

| Infant | Sex | Birth | | Study | | Major diagnoses during neonatal period |
|--------|-----|------------|----------------------|------------|--------------------------|--|
| | | Weight (g) | Gestational Age (wk) | Weight (g) | Post-conception age (wk) | |
| 1 | F | 875 | 28 | 1670 | 38 | HMD, PDA, apnea, polycythemia |
| 2 | F | 1115 | 27 | 1880 | 36 | HMD, PDA, apnea, CLD |
| 3 | M | 1130 | 28 | 2100 | 39 | CLD, PDA, pulmonary hemorrhage |
| 4 | F | 1150 | 27 | 1940 | 35 | PDA |
| 5 | F | 1160 | 29 | 2610 | 40 | HMD, PDA, apnea, ICH, hydrocephalus |
| 6 | F | 1190 | 30 | 2480 | 41 | PDA |
| 7 | F | 1200 | 32 | 1790 | 37 | HMD, PDA |
| 8 | F | 1330 | 35 | 1850 | 40 | ICH, PDA, aspiration pneumonia |
| 9 | F | 1775 | 37 | 1940 | 42 | CLD, PDA, meconium aspiration |
| 10 | M | 2820 | 39 | 2730 | 41 | HMD, ICH |
| 11 | F | 3330 | 40 | 3170 | 42 | Unexplained cyanotic spell |
| 12 | F | 3740 | 41 | 3480 | 42 | Polycythemia |

apnea – episodes of apnea requiring external stimulation

CLD – chronic lung disease

ICH – intracranial hemorrhage

PDA – patent ductus arteriosus

HMD – hyaline membrane disease

the case of hydrocephalus had a ventricular-peritoneal shunt

and occipital areas of the scalp; at the outer canthus of each eye; over the anterior third of the mandible bilaterally, on each shoulder, and a single reference electrode over the upper thoracic spine, for continuous recording of the electroencephalogram (EEG), electroculogram (EOG), electromyogram (EMG) and electrocardiogram (ECG) respectively, on a Beckman Type-T electroencephalograph (Fig. 1). A small temperature-sensitive probe at the external nares detected respiratory pattern and the investigators observed and reported movements of the eyes, face, and limbs.

Active and quiet sleep were identified using the criteria of ANDERS et al. [1]. Fig. 2 displays typical active and quiet sleep polygraph recordings. As noted by PARMALLEE [15], some infants do not have all of the characteristic findings of active or quiet sleep. For identification of the sleep state as active or quiet we required characteristic EEG, EOG, and patterns of body movements; all other sleep was classified as indeterminate and as a consequence, we rejected many studies which are not included in this analysis.

During each 2 to 3 hour sleep study we withdrew four to six 0.4 ml samples of arterial blood into

1 ml heparinized syringes over 5 to 10 seconds, after infants had been in active or quiet sleep for at least one minute. When the procedure disturbed the infant and changed his sleep state, the samples were not included in our study. For this reason, and since, in the newborn infant, variables change asynchronously making the point of transition

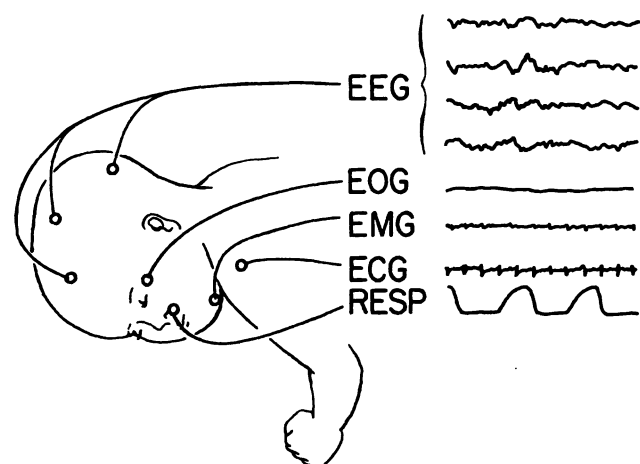


Fig. 1. Placement of electrodes for recording EEG (electroencephalogram), EOG (electroculogram), EMG (electromyogram), ECG (electrocardiogram), and RESP (respiratory pattern).

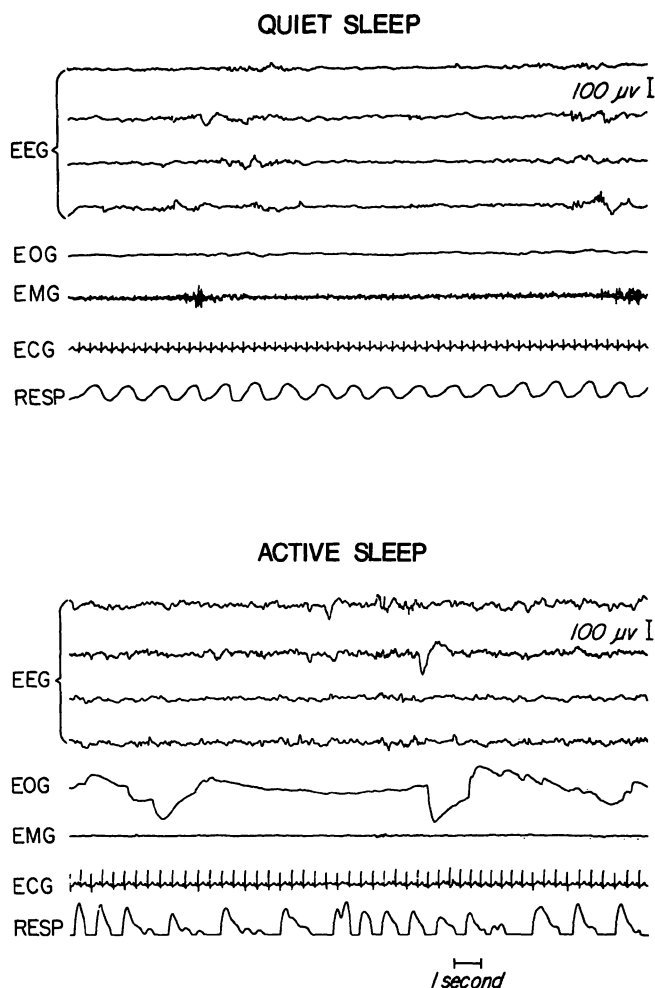


Fig. 2. Representative polygraph records from quiet and active sleep

between sleep state difficult to determine, we were unable to sample at a standard time after the infants entered each sleep state. However, we did attempt to sample alternatively from active and quiet sleep during the study.

On 7 occasions we withdrew samples of blood at two different times during the same period of active sleep to determine if arterial oxygen and carbon dioxide tensions (PaO_2 and PaCO_2) change during periods of active sleep. The mean interval between these paired samples was 11.6 minutes (SD 2.7).

We measured the arterial pH, PaO_2 and PaCO_2 with a Radiometer microblood gas system within 5 minutes of the sampling procedures and corrected them to the infant's rectal temperature [19]. The 95 percent confidence limits of these measurements

were ± 1.2 torr for oxygen, ± 1.7 torr for carbon dioxide and $\pm .002$ for pH. The electrodes were calibrated before and after each blood analysis. The duration of all respiratory pauses of two seconds or more was measured and the mean frequency and duration of these pauses calculated.

We used STUDENT's *t* test for dependent pairs to analyze the mean differences in PaCO_2 , and respiratory pauses between quiet and active sleep, the WILCOXON signed rank test to analyze the mean differences in PaO_2 and pH between quiet and active sleep, and FISHER's exact test [9] to detect correlations between blood gases, respiratory pauses and other clinical data.

3 Results

PaO_2 was lower during active than during quiet sleep in 10 of the 12 infants studied, in one PaO_2 rose, and in one there was no change (Tab. II).

The median difference was 2 torr ($P < .01$) with a range from +3 to -10 torr. A quiet to active sleep difference in PaO_2 of more than 1.5 torr correlated significantly with longer respiratory pauses during active sleep and during the entire study independent of sleep state ($P = .002$) by FISHER's exact test.

There was no significant correlation of the change in PaO_2 from active to quiet sleep with birth weight or gestational age, weight, postconceptional, or postnatal age at study, PaCO_2 , or with a history of respiratory distress syndrome, hydrocephalus secondary to intracranial hemorrhage, or recurrent apneic episodes necessitating stimulation. The difference in PaCO_2 between quiet and active sleep was +3 to -3 torr which was not significant.

The arterial pH was higher during active than quiet sleep in 10 of 12 subjects (Tab. II) with a median difference of .01 pH units ($P < .01$), but there was no significant relation of sleep state pH differences to postnatal, postconceptional or gestational age or PaCO_2 .

In the seven studies in which arterial blood was obtained twice during a single period of active sleep, the mean rate of fall of PaO_2 was 0.3 torr/minute (SD 0.3). We did not have sufficient data to analyze the change of PaO_2 during quiet sleep. The average intervals between onset of sleep state

Tab. II. Average pH and arterial oxygen and carbon dioxide tension (pO₂ and pCO₂) and frequency and duration of respiratory pauses of two seconds or longer.

| Infant | Quiet Sleep | | | | | Active Sleep | | | | |
|--------|-----------------|------------------|------|-----------------------------------|-----------------------------|-----------------|------------------|------|-----------------------------------|-----------------------------|
| | pO ₂ | pCO ₂ | pH | Fre- quency (pauses/ hr) | Pauses Duration (sec) | pO ₂ | pCO ₂ | pH | Fre- quency (pauses/ hr) | Pauses Duration (sec) |
| 1 | 65 | 37 | 7.41 | 17.6 | 4.6 | 63 | 40 | 7.42 | 64.5 | 4.0 |
| 2* | 65 | 36 | 7.43 | 0 | 0 | 63 | 35 | 7.43 | 40.3 | 4.4 |
| 3 | 72 | 41 | 7.37 | 10.6 | 5.0 | 70 | 39 | 7.38 | 92.5 | 4.3 |
| 4 | 65 | 38 | 7.39 | 187.0 | 6.9 | 60 | 39 | 7.40 | 158.4 | 5.8 |
| 5 | 55 | 40 | 7.34 | 4.3 | 4.5 | 54 | 41 | 7.39 | 45.4 | 3.1 |
| 6 | 67 | 45 | 7.40 | 9.0 | 3.8 | 70 | 44 | 7.41 | 13.0 | 2.7 |
| 7 | 76 | 39 | 7.38 | 23.8 | 4.6 | 66 | 39 | 7.39 | 93.6 | 4.2 |
| 8 | 65 | 39 | 7.39 | 26.3 | 4.2 | 55 | 36 | 7.40 | 44.3 | 4.1 |
| 9 | 49 | 46 | 7.40 | 29.2 | 4.0 | 48 | 48 | 7.39 | 49.0 | 3.3 |
| 10 | 59 | 46 | 7.39 | 39.0 | 5.0 | 56 | 44 | 7.40 | 99.0 | 5.4 |
| 11 | 87 | 40 | 7.39 | 49.0 | 4.8 | 83 | 40 | 7.40 | 174.0 | 5.0 |
| 12* | 74 | 35 | 7.39 | 0 | 0 | 74 | 34 | 7.42 | 14.4 | 3.0 |
| Mean | 67 | 40 | 7.39 | 33.0 | 4.0 | 64 | 40 | 7.40 | 74.0 | 4.1 |
| SD | 10 | 4 | 0.02 | 50.9 | 2.0 | 10 | 4 | 0.02 | 51.6 | 1.0 |

Each pO₂ and pCO₂ value represents an average of 1–3 determinations.

*These patients had no respiratory pauses of 2 seconds or more during quiet sleep.

and time of sampling in quiet and active sleep were 8.4 minutes (SD 7.3) and 11.4 minutes (SD 6.5), respectively, ($P > 0.2$). The average rate of change of PaO₂ during the total sleep study, independent of sleep state, was an increase of 1.2 torr/hour (SD 4.2).

The mean frequency and duration of respiratory pauses of two seconds or longer, during active and quiet sleep are listed in Tab. II. **These respiratory pauses were more frequent in active than in quiet sleep ($P < .005$).** Infants of eight weeks postnatal age or less, or of 38 weeks postconceptional age or less had significantly more respiratory pauses than older infants ($P < .025$). There was no significant correlation between respiratory pauses and PaCO₂, gestational age, birthweight, or current or past illnesses.

4 Discussion

This study provides data on sleep state, respiratory pauses and arterial blood gases and pH from undisturbed, sleeping newborn and young infants. We studied a select group of subjects, most of whom

were born prematurely and had chronic lung disease, and therefore the results are not necessarily applicable to normal infants.

The median PaO₂ decrease of 2 torr between quiet and active sleep was probably of little physiological significance in these infants. All PaO₂ values obtained during active sleep were above 45 torr, a level which would be unlikely to cause central depression of respiration. We feel this change in oxygenation is probably due to sleep state itself since such other determinants of respiratory pattern as temperature and external stimuli were constant throughout our study. In a larger study group these small sleep state differences in PaO₂ might not be statistically significant. However, two of the infants in this study had differences of 10 torr, indicating the potential for a physiologically significant fall in PaO₂ during active sleep in some infants.

Since the measurement of pH is more precise than that of PaCO₂ (coefficients of variation are .014 percent and 2.14 percent respectively in our laboratory), the relative alkalemia found during active sleep could be due to slight alveolar hypoventilation which is not reflected in the less precise

PaCO₂ measurement. Therefore, we interpret our data to indicate that during active sleep these infants either had no change or an increase in alveolar ventilation and that the drop in oxygen tension was not caused by hypoventilation. Others have also found evidence of increased alveolar ventilation during REM sleep [3, 4].

The most likely explanation for the increased hypoxemia of active sleep is a change in the distribution of ventilation during active sleep. KNILL et al. [13] have documented greater rib cage distortion during active sleep, and they have suggested that this may cause local variation in pleural pressure, thereby contributing to in-

equalities in regional ventilation. The increase in oxygen consumption in active sleep [18] might also contribute to the lower PaO₂ at that time.

The greater incidence of respiratory pauses in active sleep has been reported by others [3, 4, 6, 7, 10, 11, 12, 20]. These pauses might promote intermittent microatelectasis with loss of lung volume [14] and increased intrapulmonary venous admixture. Our finding of a significant ($p = .002$) correlation between longer mean respiratory pauses and a greater quiet to active sleep fall in PaO₂ is consistent with a loss of lung volume as part of the mechanism causing the relative hypoxemia of active sleep.

Summary

We studied the relationship between sleep state, and arterial blood gases and pH, in 12 newborn and young infants (Tab. I), 11 of whom had mild chronic lung disease, in order to determine whether significant arterial hypoxemia occurred during active sleep. Such hypoxemia, were it to occur, could theoretically cause central depression or instability of the effective output of the respiratory center, and thus might explain the irregular respiratory patterns and prolonged apnea which may be seen during active sleep. All the subjects were less than 44 weeks postconceptional age, 9 were born prematurely, and 11 had a sleeping arterial oxygen tension (PaO₂) while breathing room air of less than 80 torr at the time of study. We classified sleep state as active or quiet by observing the infant's body movements, electroencephalogram, electrooculogram and electromyogram (Fig. 1). Respiratory pattern was obtained from a temperature sensitive probe placed at the external nares. When infants were in active or quiet sleep (Fig. 2) we drew blood samples from an indwelling cannula in a superficial temporal artery which did not appear to disturb them. During active sleep, median PaO₂ was 2 torr lower

($P < .01$), pH 0.01 higher ($P < .05$), and respiratory pauses more frequent ($P < .005$) than during quiet sleep (Tab. II). Greater sleep PaO₂ differences were seen in infants with longer respiratory pauses. Arterial carbon dioxide tension was not affected by sleep state, nor was it related to the frequency or duration of respiratory pauses. We suggest that the fall in PaO₂ associated with active sleep is most likely a reflection of altered distribution of ventilation caused by greater chest wall instability and by loss of lung volume with resultant increased venous admixture during the more frequent respiratory pauses during active as compared to quiet sleep. The median PaO₂ decrease of 2 torr between quiet and active sleep is small and is probably of little physiological significance in this group of subjects. Since all PaO₂ values obtained during active sleep were above 45 torr, we doubt that these subjects are at risk of central hypoxic depression of respiratory drive during active sleep. Since we studied a select group of subjects, most of whom were prematurely born and had mild chronic lung disease, our results are not necessarily applicable to normal infants.

Keywords: Arterial blood gases, control of breathing, infants, respiratory pause, sleep state.

Zusammenfassung

Arterielle Blutgas- und pH-Werte während des Schlafstatus bei menschlichen Neugeborenen und jungen Säuglingen.

Untersucht wurde der Zusammenhang zwischen Schlafstatus und arteriellen Blutgas- bzw. pH-Werten bei 12 Neugeborenen und jungen Säuglingen (Tab. I), von denen 11 eine leichte chronische Lungendysfunktion aufwiesen. Es galt zu bestimmen, ob es während der „aktiven“ Schlafphase zu einer signifikanten arteriellen Hypoxämie kommt. Falls eine solche Hypoxämie auftreten würde, könnte diese theoretisch die Ursache für einen Rückgang oder eine Instabilität der effektiven Leistung des Atemzentrums darstellen, und dies könnte wiederum unregelmäßige Atmungskurven sowie die länger andauernden Apnoen er-

klären, wie sie während des aktiven Schlafs gefunden werden. Das postkonzeptionelle Alter aller untersuchten Kinder war niedriger als 44 Wochen; 9 wurden als prä-matur eingestuft, und bei 11 der 12 untersuchten Kinder betrug der arterielle O₂-Partialdruck (pO₂) bei Einatmung von Zimmerluft im Schlafstatus weniger als 80 Torr. Für die Klassifikation „aktiver Schlaf“ bzw. „Tiefschlaf oder ruhiger Schlaf“ zogen wir folgende Kriterien heran: kindliche Körperbewegungen, Elektroenzephalogramm, Elektrokulogramm sowie das Elektromyogramm (Fig. 1). Die Atmungskurven wurden mittels temperatursensitiver Sonden, die außen an den Nasenflügeln angebracht waren, aufgezeichnet. Die Entnahme der Blutproben bei den

Kindern im aktiven bzw. im Tiefschlaf erfolgte über eine Kanüle in einer oberflächlichen Schläfenarterie, was keine großen Störungen zu verursachen schien. Während des aktiven Schlafs war der mittlere pO_2 um 2 Torr niedriger ($p < .01$), der pH um 0.01 höher ($p < .05$) sowie Atempausen weitaus häufiger ($p < .005$) als während des Tiefschlafs. Je länger die Atempausen waren, umso stärker differierten die pO_2 -Werte. Der arterielle CO_2 -Partialdruck erfuhr weder eine Änderung während des Schlafstatus noch ließ er sich in eine Beziehung zur Häufigkeit bzw. Länge der Atempausen setzen. Der in Verbindung mit dem aktiven Schlaf gefundene Abfall des pO_2 ist damit unserer Meinung nach am ehesten zurückzuführen auf eine geänderte Verteilung der Ventilation, die ihrerseits durch größere Brustkorbinstabilität und verringertes Atemvolumen verursacht wird. Die im Ver-

gleich mit dem Tiefschlaf weitaus häufigeren Atempausen während des aktiven Schlafstatus ziehen dann eine Zunahme der venösen Durchmischung nach sich. Die Abnahme des pO_2 um 2 Torr im Tiefschlaf gegenüber dem aktiven Schlaf ist gering und sehr wahrscheinlich von unwesentlicher physiologischer Bedeutung in unserem Untersuchungskollektiv. Da alle pO_2 -Werte während des aktiven Schlafstatus über 45 Torr lagen, halten wir es für unwahrscheinlich, daß die untersuchten Kinder während dieser Phase dem Risiko einer durch eine Hypoxie bedingten Verminderung des Atemantriebs ausgesetzt sind. Unsere Ergebnisse sind nicht unbedingt auf gesunde Kinder zu übertragen, da wir ein selektiertes Kollektiv untersuchten, in dem die meisten Kinder prämaturn geboren waren und leichte chronische Lungenkomplikationen aufwiesen.

Schlüsselwörter: Arterielle Blutgaswerte, Atemkontrolle, Atempausen, Säuglinge, Schlafstatus.

Résumé

Etat de sommeil et gaz et pH du sang artériel chez les nouveaux-nés et bébés humains

Nous avons étudié les rapports entre l'état de sommeil et les gaz et pH du sang artériel de 12 nouveaux-nés et bébés (Tab. I) — dont 11 souffraient de légers troubles pulmonaires chroniques — afin d'observer si une hypoxémie artérielle importante pouvait se produire pendant le sommeil actif. Une telle hypoxémie, au cas où elle se produirait, pourrait théoriquement provoquer une dépression centrale ou une instabilité du débit effectif du centre respiratoire, ce qui expliquerait éventuellement ces courbes de respiration irrégulière et d'apnée prolongée qu'on enregistre parfois pendant le sommeil actif. Tous les sujets étaient âgés de moins de 44 semaines, 9 étaient nés prématurément et 11 avaient une tension artérielle d'oxygène en sommeil (PaO_2) tandis que l'air ambiant de respiration était inférieur à 80 torr au moment de l'étude. Nous avons qualifié l'état de sommeil d'actif ou de calme selon les résultats enregistrés des mouvements du corps de l'enfant, de l'électroencéphalogramme, de l'électrooculogramme et de l'électromyogramme (fig. 1). Les courbes respiratoires ont été obtenues à l'aide d'une sonde sensible à la température et placée aux narines externes. Les enfants étant en sommeil actif ou calme (fig. 2), nous avons prélevé des spécimens sanguins à l'aide d'une canule maintenue dans une artère temporale superficielle et qui n'a pas paru troubler les sujets. Pendant le sommeil actif, le PaO_2

moyen a été de 2 torr inférieur ($p < .01$), le pH de 0,01 supérieur ($p < .05$) et les pauses respiratoires plus fréquentes ($p < .005$) qu'en cours de sommeil calme (Tab. II). Des différences plus grandes de PaO_2 en sommeil ont pu être observées chez les enfants avec des pauses respiratoires plus longues. La tension de dioxyde de carbone artériel n'a pas été affectée par l'état de sommeil et s'est montrée indépendante de la fréquence ou de la durée des pauses respiratoires. Nous supposons que la baisse de PaO_2 associée au sommeil actif est le plus probablement le reflet d'une distribution altérée de ventilation causée par une plus grande instabilité de la paroi thoracique et par la perte du volume pulmonaire avec une admixture veineuse accrue résultante durant les pauses respiratoires plus fréquentes pendant le sommeil actif en comparaison avec le sommeil calme. La différence moyenne de PaO_2 de 2 torr entre le sommeil actif et calme n'est pas grande et est probablement de peu d'importance physiologique dans ce groupe de sujets. Etant donné que toutes les valeurs de PaO_2 obtenues durant le sommeil actif ont été supérieures à 45 torr, nous doutons que ces sujets courent un risque de dépression hypoxique centrale du débit respiratoire durant le sommeil actif. Notre groupe de sujets se composant pour la plupart d'enfants prématurés avec de légers troubles pulmonaires chroniques, nos résultats ne s'appliquent pas nécessairement à des bébés normaux.

Mots-clés: Bébé, contrôle de la respiration, état de sommeil, gaz du sang artériel, pause respiratoire.

Acknowledgement: This work was supported by program Project Grant HL 7285 and Training Grant HL 05251 from the National Heart and Lung Institute

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Received November 2, 1977. Revised January 1978,
Accepted May 14, 1978.

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