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# Sleep, Respiratory Rate, and Growth Hormone in Chronic Neonatal Lung Disease

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**Summary.** This study assessed whether respiratory rates (RRs) correlate with urinary growth hormone (U-GH) excretion and sleep architecture in infants with chronic neonatal lung disease (CNLD) in early (1 month), middle (6 months), and late (10 months) infancy. Twenty-three preterm infants (CNLD = 16, controls = 7) were studied on 51 occasions. CNLD infants were stratified according to mean non-REM sleep respiratory rate (NREM RR) in early infancy into ''High RR CNLD'' infants (mean NREM RR >2 SD higher than controls) and ''Normal RR CNLD'' infants (mean NREM RR within 2 SD of controls' mean).

''High RR CNLD'' infants (RR >45) had a lower mean birthweight ($P = 0.015$), current weight ($P = 0.042$), current length ($P = 0.02$), and growth velocity in early infancy (grams/week gained: $P = 0.042$) than ''Normal RR CNLD'' and control infants. Mean (95% CI) U-GH excretion (ng U-GH/g urinary creatinine) was higher in ''High RR CNLD'' infants in air or their usual $O_2$ (1,932 [459, 3,406]) than ''Normal RR CNLD'' (394 [147, 642]) and controls (320 [147, 492]) ($P = 0.024$). With resolution of tachypnea by mid-infancy, hemoglobin oxygen saturation ($SaO_2$) >93%, mean growth parameters and U-GH excretion for the ''High RR CNLD'' group were not significantly different from ''Normal RR CNLD'' and control groups. CNLD infants demonstrated increased sleep efficiency ($P = 0.016$), whereas controls had similar sleep efficiency between early and middle infancy ($P = 0.452$). Mean percent time in REM sleep (REM%) and slow wave sleep (SWS%) were not significantly different between early and middle infancy and did not vary in relation to respiratory rate. We conclude that tachypneic infants with CNLD have slower growth and elevated U-GH excretion in early infancy. With resolution of tachypnea, growth improved, U-GH excretion decreased, and sleep consolidation occurred. An elevated U-GH in tachypneic CNLD infants may reflect stress, compromised nutrition (GH resistance), or a feedback loop involving a direct effect of GH on lung growth and repair. **Pediatr Pulmonol. 1998; 26: 241–249.** 

**Key words: growth hormone; sleep architecture; respiratory rate; chronic neonatal lung disease.**

## INTRODUCTION

Tachypnea, increased work of breathing and poor growth, commonly occur in infants with chronic neonatal lung disease (CNLD).[1–3] Poor growth has been attributed to preterm delivery at very low birthweight,[4] concurrent morbidity,[3,4] and severity of lung disease[5,6]. The association between growth limitation and severe lung disease is supported by the demonstration of tachypnea and elevated minute ventilation in CNLD infants with failure to thrive.[2,7] While higher oxygen ($O_2$) consumption is present in CNLD infants with greater work of breathing and higher metabolic rates,[8,9] it is unlikely to be the only explanation for poor weight gain in CNLD infants with severe lung disease.[3,10] Alternatively, growth impairment may occur as a consequence of hypoxemia-induced appetite suppression[1,3] and neurohumoral stimulation,[11] with raised levels of endogenous catecholamines causing a hypermetabolic state with impaired glucose and lipid metabolism.[3]

The mechanism by which growth is limited in the tachypneic infants with severe lung disease is unknown. A potential regulator is growth hormone (GH), recently suggested to play an important role in perinatal and infantile growth.[12–14] Serum GH levels are detectable in fetuses as early as 8 weeks, rising to a peak in fetal life at 20–24 weeks (approximately 120 ng/ml) before declining until term (25–30 ng/ml) when they are in the

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range seen in acromegalics.[15] Postnatally, GH concentration falls to the basal level characteristic of the prepubertal child by 3 months of age.[15–17] Neonatal GH deficiency is recognized in multiple pituitary hormone deficiency,[13] although the presentation of congenital isolated GH deficiency is less dramatic, being associated with prenatal and early postnatal growth failure.[12,14]

Recently, the demonstration of disrupted sleep architecture in ''adequately'' oxygenated ($SaO_2$ >93%) CNLD infants with failure to thrive[18] prompted us to evaluate GH secretion in CNLD infants with poor growth. We hypothesized that CNLD infants with poor growth produce less GH due to disrupted sleep architecture. We chose decreased sleeping respiratory rates (RRs) and standard growth parameters as readily measurable clinical markers of recovery in CNLD. To overcome the difficulties of repeated blood sampling in young infants, we used multiple urine-GH (U-GH) assays in the same patients, a method validated against pharmacological stimulation tests of human GH production in the absence of renal dysfunction.[19–22] The aim of this study was to determine whether GH excretion correlated with somatic growth and sleep architecture in infants with CNLD.

Abbreviations

| | |
|---|---|
| ANOVA | Analysis of variance |
| CI | Confidence intervals |
| Cr | Creatinine |
| CNLD | Chronic neonatal lung disease |
| ECG | Electrocardiogram |
| EEG | Electroencephalogram |
| EOG | Electro-oculogram |
| GH | Growth hormone |
| High RR CNLD | High respiratory rate (frequency) infants with CNLD with an NREM sleep respiratory frequency >45 breaths/min in air or usual $O_2$ in early infancy |
| HMD | Hyaline membrane disease |
| IGF-1 | Insulin-like growth factor type 1 |
| ILD | Immature lung disease |
| Normal RR CNLD | Normal respiratory rate (frequency) infants with CNLD (frequency <45 in early infancy) |
| NREM | Non-REM |
| $O_2$ | Oxygen |
| PCA | Postconceptual age |
| RDS | Respiratory distress syndrome |
| REM | Rapid eye movement |
| REM% | Percentage of time asleep spent in REM sleep |
| ROP | Retinopathy of prematurity |
| RR | Respiratory rate |
| $SaO_2$ | Arterial oxygen saturation |
| SWS | Slow wave sleep |
| SWS% | Percentage of sleep time spent in slow wave sleep |
| $TcCO_2$ | Transcutaneous carbon dioxide tension |
| $TcO_2$ | Transcutaneous oxygen tension |
| U-GH | Urinary growth hormone excretion |

## PATIENTS AND METHODS

Twenty-three preterm subjects (CNLD = 16, controls = 7) were enrolled in a longitudinal study of sleep architecture, cardiorespiratory parameters, growth, and GH excretion during infancy. The sleep architecture findings in early infancy (1 month corrected age) in relation to hemoglobin oxygen saturation ($SaO_2$) are reported in detail in an accompanying publication.[23] CNLD was defined using a modified definition of Shennan et al.[24] as continued $O_2$ dependency at a postconceptual age (PCA) of 36 weeks.[25] The seven controls comprised four patients without lung disease and three who had initial mild respiratory distress but did not require supplemental $O_2$ beyond a PCA of 36 weeks. All patients received iron and vitamin supplements, but no patient received any medication known to interfere with GH levels.

Mean RRs were calculated from analysis of each epoch of non-rapid eye movement (NREM) sleep. Patients underwent standard overnight polysomnography in the Sleep Laboratory at The Royal Alexandra Hospital for Children in Sydney. We utilized a 16 channel Grass Polygraph Recorder (Grass Instrument Company, Quincy, MA, USA). Sleep was recorded using gold cup electrodes with two channels of electroencephalogram (EEG; C3/A2, O2/A1, 10-20 international placement system), two channels of electro-oculogram (EOG; ROC/A1, LOC/A2) and submental electromyogram (EMG). Diaphragm and abdominal muscle EMGs were similarly recorded. The electrocardiograph (ECG) and heart rate were recorded continuously. Transcutaneous oxygen ($TcO_2$) and carbon dioxide tensions ($TcCO_2$) were measured (Radiometer, TCM 3, Copenhagen, Denmark). To distinguish between central and obstructive apnea, nasal airflow was measured with a pressure transducer in the nasal prongs (Validyne, DP103, CD 316 Miniature Carrier Demodulator) and diaphragm displacement (chest and abdominal wall movements) using inductance plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, NY). Continuous oximetry was also recorded (Ohmeda, Biox 3700E pulse Oximeter). The following variables were used according to our laboratory practice and represent minor modifications of existing definitions[26,27] (see Appendix, Definitions): sleep efficiency, sleep time, REM%, REM arousal index, REM epoch duration, percent slow wave sleep (SWS%), and SWS epoch duration. Apnea of >5 sec duration (central, mixed and obstructive) was scored. Hypopneas were not scored.

During each study, urine samples were collected using adhesive bags with incorporated feeding tubes to allow withdrawal of voided urine without disturbing the patient. Urine was collected at 4-hr intervals (n = 3 or 4 per patient per night) for U-GH assay. Multiple samples rather than a single 12-hr sample were collected overnight in an attempt to determine whether U-GH excretion

was consistent overnight.[20,21,28–30] Each sample was divided by the corresponding measured urinary creatinine (Cr) to allow for potential variations in renal function, and the mean U-GH/g Cr per patient was calculated. Individual means were used to calculate means for the three groups (High RR CNLD, normal RR CNLD, and controls). Urine samples were stored at −70°C prior to transfer to the Princess Margaret Hospital for Children in Perth, Western Australia, for analysis (U-GH assays: ''Norditest,'' Novo Nordisk, Denmark, and standard urinary Cr assays).

Infants with CNLD and controls were studied in early infancy (1 month corrected age) and in middle infancy (6 months). CNLD infants were also studied in later infancy (10 months). The detailed results of sleep architecture for paired study nights in early infancy in air or usual inspired $O_2$ vs. higher inspired $O_2$ are reported separately.[23] In brief, this demonstrated that a target $SaO_2$ >93% was as efficacious as an $SaO_2$ >97% in optimizing sleep architecture in infants with CNLD in early infancy. In contrast, the present study details the evolution of sleep architecture in infancy and examines the relationship between tachypnea, sleep architecture, U-GH excretion, and growth parameters in infants with CNLD.

Analysis of variance, *t*-tests, Wilcoxon Rank test of medians, and Neuman-Keuls calculations were used in analyzing the data. A *P*-value of <0.05 was considered statistically significant, a trend was suggested by a *P*-value <0.05 and 0.10, and a *P*-value >0.10 was considered not significant (NS). The Royal Alexandra Hospital for Children Ethics Review Committee granted approval for this study. Parents could withdraw their children from the study at any time.

## RESULTS

### Demographics

There was no difference in the median (range) gestational age between infants with CNLD (28.8 weeks [24–31]) and controls (29.2 weeks [26–33]) (Wilcoxon rank test; $P = 0.280$). However, CNLD infants had a lower median (range) birthweight (986 g [500–1,490]) than controls (1,559 g [790–2,085]) ($P = 0.031$). There were two growth retarded infants (birthweight <10%) in the nontachypneic CNLD group and two in the tachypneic CNLD group. All controls were appropriately grown for their gestation. At the time of the initial study (night 1), 11/16 CNLD infants were in air and the remainder (n = 5) were receiving supplemental $O_2$ (range 0.125–0.75 L/min). All 23 subjects (CNLD = 16; controls = 7) completed studies in early infancy and 74% (CNLD = 12; controls = 5) completed a study in middle infancy. In addition, 11/16 CNLD infants (69%), but no controls, had studies in late infancy. The reasons for withdrawal were normal polysomnographic studies in three infants, parental concern about ''excessive testing'' in three infants, and family relocation in the other infant. The gestational age, birthweight, and current weight of the subjects who withdrew did not differ from those who had subsequent studies.

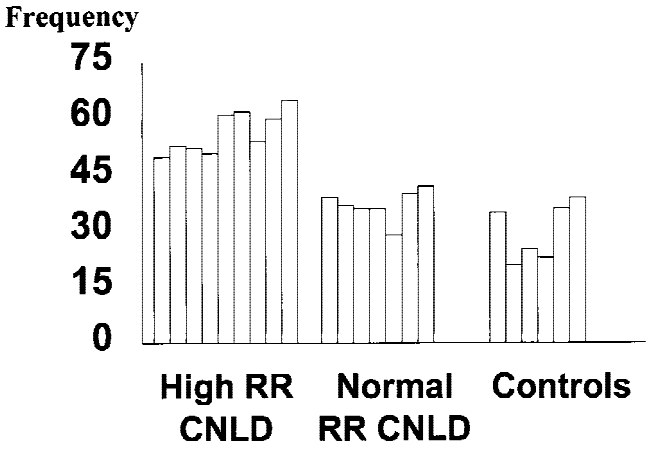


**Fig. 1. Histogram of the non-REM sleep mean respiratory rates by groups in early infancy.**

In addition, in early infancy higher inspired $O_2$ than usual was administered on a separate study night for all 23 subjects. The U-GH data are the only data considered in this article from the higher inspired $O_2$ night in early infancy. Urine was collected on 98% (62/63) study nights in early and middle infancy (early infancy 23 + 22 and middle infancy 17). Parents declined urine collection for one control in the higher inspired $O_2$ night in early infancy because of a diaper rash.

### Cardiorespiratory Parameters

#### Early Infancy

The mean (±SD) NREM sleep respiratory frequency was significantly higher for all 16 CNLD patients than for controls on night #1 in air or usual supplemental $O_2$ (47.5 ± 10.7 vs. 31.2 ± 6.7, $P < 0.0001$). In 0.25 L/min additional supplemental inspired $O_2$, the mean respiratory frequency for both CNLD infants (47.5 ± 10.7 vs. 42.6 ± 9.3; $P = 0.003$) and controls (31.2 ± 6.7 vs. 28.8 ± 8.0; $P = 0.019$) fell significantly. Analysis of the NREM respiratory frequency for CNLD infants in air/usual $O_2$ revealed two clearly differing subgroups of high respiratory frequencies and similar frequencies to controls (Neuman-Keuls test of simultaneous inference; $P < 0.05$).[31] Consequently, CNLD NREM respiratory frequency data was reanalyzed with CNLD infants subdivided into two groups (''High RR CNLD'' and ''Normal RR CNLD'') according to their mean NREM sleep respiratory frequency in air/usual level of supplemental $O_2$ in early infancy (Fig. 1). Tachypnea (''High RR'') was

**TABLE 1—Variables in Sleep Architecture for Infants With Chronic Neonatal Lung Disease and High Respiratory Rates**

| High RR CNLD Mean (±SD) | Early infancy 1 month (n = 9) | Middle infancy 6 months (n = 5) | Late infancy 10 months (n = 4) | ANOVA |
|---|---|---|---|---|
| Sleep efficiency (%) | 61 (9.6) | 83 (5.1) | 78 (11) | $P = 0.001$ |
| Sleep time (min) | 366 (59) | 486 (53) | 431 (53) | $P = 0.004$ |
| Awake time (min) | 234 (65) | 99 (37) | 121 (66) | $P = 0.002$ |
| REM sleep % | 30.0 (8.1) | 37.0 (5.5) | 30.4 (8.8) | $P = 0.094$ |
| REM arousal index | 18.3 (7.0) | 13.2 (3.4) | 9.2 (1.1) | $P = 0.031$ |
| REM epoch duration | 12.8 (2.4) | 18.3 (2.7) | 17.4 (4.1) | $P = 0.007$ |
| SWS% | 33 (14) | 39 (6.1) | 37.2 (6.1) | $P =$ NS |
| SWS epoch duration | 19.4 (8.7) | 22.6 (2.7) | 27.8 (2.8) | $P =$ NS |

For abbreviations and definitions see Abbreviations and Appendix, respectively.

present in CNLD infants when the mean NREM respiratory frequency was >45 breaths/min. This was based on mean respiratory frequency being two standard deviations higher than the mean for the seven preterm controls. There were nine tachypneic (''High RR CNLD'') infants (54.4 ± 6.6) and seven (''Normal RR CNLD'') nontachypneic (37.6 ± 6.4) infants. All 23 infants had baseline (early infancy) NREM sleep $SaO_2$ >93%. The mean NREM $SaO_2$ and heart rates did not differ between groups during subsequent studies. The mean transcutaneous $CO_2$ remained at <50 torr and did not differ between groups.

### Middle and Late Infancy

By mid-infancy, there was no difference in mean RRs between the originally tachypneic CNLD, nontachypneic CNLD, and control groups. There was no distinction in mean $TcCO_2$, $SaO_2$ (>93%), or heart rate between the groups.

## Sleep Architecture

Of the 16 infants with CNLD, 11 (69%) had studies in early, middle, and late infancy. All withdrawals were from the High RR CNLD group. For all CNLD infants, mean (SD) sleep efficiency improved (70.5% [14.6] vs. 84.4% [5.4] vs. 80.3% [10.7]; $P = 0.016$) and waking time after sleep onset decreased (167 min [92] vs. 86 min [37] vs. 107 min [61]; $P = 0.022$) with increasing age. When this was analyzed in relation to respiratory frequency, the improvement in sleep efficiency was evident only in High RR CNLD infants (Tables 1 and 2 [subset of four who had all studies]). Sleep efficiency and waking time were not significantly different for Normal RR CNLD infants (Table 3) and controls (Table 4). For all CNLD infants, there were increases in mean duration for epochs of REM sleep without changes in REM%, SWS%, or SWS epoch mean duration (Tables 1, 3). The REM arousal index in CNLD infants fell with time (Tables 1, 2, 3). In contrast, the control group did not manifest changes in sleep efficiency, waking time, REM%, SWS%, REM epoch mean duration, SWS mean epoch duration, or REM arousal index between early and middle infancy (Table 4). There were no central apneas of >20 sec duration measured in this study. No patients had obstructive apnea in middle or late infancy and the only subject with obstructive apnea in early infancy was withdrawn from the study by parental request after the paired studies in early infancy.

**TABLE 2—Sleep Architecture in the Four Infants With Chronic Neonatal Lung Disease and High Respiratory Rate and Studies in Early, Middle, and Late Infancy**

| High RR CNLD Mean (±SD) | Early infancy 1 month (n = 4) | Middle infancy 6 months (n = 4) | Late infancy 10 months (n = 4) | ANOVA |
|---|---|---|---|---|
| Sleep efficiency (%) | 62 (15) | 83 (5) | 78 (11) | $P = 0.027$ |
| Sleep time (min) | 344 (62) | 478 (67) | 431 (53) | $P = 0.013$ |
| Awake time (min) | 220 (106) | 99 (37) | 121 (66) | $P = 0.057$ |
| REM sleep % | 31.5 (5.5) | 34.5 (9.8) | 30.4 (8.8) | $P =$ NS |
| REM arousal index | 18.1 (8.5) | 13.0 (3.7) | 9.2 (1.1) | $P = 0.064$ |
| REM epoch duration | 13.4 (3.0) | 17.4 (3.2) | 17.4 (4.1) | $P =$ NS |
| SWS% | 34.6 (5.2) | 39.2 (6.1) | 37.2 (6.1) | $P =$ NS |
| SWS epoch duration | 21.9 (5.6) | 25.0 (3.9) | 27.8 (2.8) | $P =$ NS |

For abbreviations and definitions see Abbreviations and Appendix, respectively.

**TABLE 3—Sleep Architecture Variables for Seven Subjects With Chronic Neonatal Lung Disease and Normal Respiratory Rate Throughout Infancy**

| Normal RR CNLD Mean (±SD) | Early infancy 1 month (n = 7) | Middle infancy 6 months (n = 7) | Late infancy 10 months (n = 7) | ANOVA |
|---|---|---|---|---|
| Sleep efficiency (%) | 78 (8.9) | 86 (6.1) | 84 (11) | $P$ = NS |
| Sleep time (min) | 428 (91) | 418 (48) | 429 (77) | $P$ = NS |
| Awake time (min) | 122 (52) | 72 (35) | 87 (59) | $P$ = NS |
| REM sleep % | 31.4 (6.4) | 27.4 (7.0) | 33.4 (10.3) | $P$ = NS |
| REM arousal index | 19.1 (6.2) | 12.2 (2.8) | 11.2 (4.8) | $P$ = 0.013 |
| REM epoch duration | 14.2 (4.0) | 15.9 (2.5) | 19.0 (3.0) | $P$ = 0.038 |
| SWS% | 36.0 (4.9) | 41.9 (11.5) | 36.8 (10.1) | $P$ = NS |
| SWS epoch duration | 21.6 (3.0) | 25.7 (5.7) | 24.2 (6.5) | $P$ = NS |

For abbreviations and definitions see Abbreviations and Appendix, respectively.

**TABLE 4—Sleep Architecture in Five Controls With Paired Studies in Early and Middle Infancy**

| Controls Mean (±SD) | Early infancy 1 month (n = 5) | Middle infancy 6 months (n = 5) | ANOVA |
|---|---|---|---|
| Sleep efficiency (%) | 66.2 (24.2) | 75.5 (10.3) | $P$ = NS |
| Sleep time (min) | 400 (153) | 466 (70) | $P$ = NS |
| Awake time (min) | 198 (132) | 152 (63) | $P$ = NS |
| REM sleep % | 35.1 (15.8) | 34.4 (10.9) | $P$ = NS |
| REM arousal index | 15.4 (7.6) | 11.0 (7.9) | $P$ = NS |
| REM epoch duration | 14.2 (7.7) | 18.3 (3.6) | $P$ = NS |
| SWS% | 35.1 (12.2) | 36.5 (7.4) | $P$ = NS |
| SWS epoch duration | 19.8 (7.3) | 22.7 (3.4) | $P$ = NS |

For abbreviations and definitions see Abbreviations and Appendix, respectively.

## Growth Parameters

High RR CNLD infants had a significantly lower mean (95% CI) birthweight (890 g [610, 1,170] vs. 1,170 g [840, 1,500] vs. 1,650 g [1,050, 2,260]; $P = 0.015$) and current weights (2,870 g [2,310, 3,440] vs. 4,180 g [3,290, 5,070] vs. 4,460 g [2,610, 6,310]; $P = 0.048$) when compared to Normal RR CNLD infants and preterm controls in early infancy. The differences in weight, length, and head circumference in middle infancy were not significant between the groups (Table 5). Velocity of weight gain (g/week) was analyzed for the three groups of infants. Significantly slower (mean ±SD) growth velocity (g/week) was seen in High RR CNLD infants between birth and early infancy (122 g/week [±45] vs. 206 [±109] vs. 169 [±78]; $P = 0.04$); there were no significant differences in the velocity of weight gain between early and middle infancy between the three groups (Table 5).

## U-GH Excretion

Mean U-GH excretion was expressed as nanograms U-GH per gram of urinary Cr because of potential differences in renal function and urine volume. There were no differences in urinary Cr excretion between groups on each of the study nights. The mean U-GH/4 hr are expressed in terms of renal function (per ng of urinary

**TABLE 5—Growth Parameters for 17 Infants With Paired Studies in Early and Middle Infancy**

| Mean (±SD) | Variable | Early infancy | Middle infancy | $P$ value |
|---|---|---|---|---|
| High RR CNLD (n = 5) | Age (months) | 2.0 (±1.4) | 6.2 (±1.2) | |
| | Weight (kg) | 3.13 (±0.91) | 5.96 (±1.45) | $P$ = 0.01 |
| | Length (cm) | 49.3 (±6.1) | 61.7 (±4.9) | $P$ = 0.03 |
| | Head circ. (cm) | 37.0 (±3.1) | 42.4 (±1.9) | $P$ = 0.04 |
| | Weight gain (g/wk) | 122 (±45) | 157 (±89) | $P$ = NS |
| Normal RR CNLD (n = 7) | Age (months) | 1.8 (±1.1) | 6.7 (±2.8) | |
| | Weight (kg) | 4.28 (±0.87) | 7.25 (±1.8) | $P$ = 0.003 |
| | Length (cm) | 52.5 (±3.6) | 65.1 (±7.0) | $P$ = 0.001 |
| | Head circ. (cm) | 38.5 (±0.5) | 43.7 (±2.5) | $P$ = 0.01 |
| | Weight gain (g/wk) | 206 (±109) | 135 (±81) | $P$ = NS |
| Controls (n = 5) | Age (months) | 2.6 (±2.2) | 6.4 (±2.4) | |
| | Weight (kg) | 5.01 (±2.16) | 7.41 (±1.72) | $P$ = 0.08 |
| | Length (cm) | 56.4 (±6.8) | 64.5 (±6.3) | $P$ = 0.09 |
| | Head circ. (cm) | 39.1 (±4.4) | 44.9 (±3.3) | $P$ = 0.05 |
| | Weight gain (g/wk) | 169 (±78) | 134 (±73) | $P$ = NS |

For abbreviations and definitions see Abbreviations and Appendix, respectively.

creatinine excreted). The mean (±SD) excretion of U-GH (ng/g Cr/4 hr) was significantly higher in early infancy in High RR CNLD infants in air/usual supplemental $O_2$ (1,932 ± 1,917) than Normal RR CNLD infants (394 ± 267) and controls (363 ± 197) (ANOVA; $P = 0.034$). We repeated the U-GH assays in higher than baseline inspired $O_2$ in early infancy for all 23 subjects (the second of paired study nights in early infancy) and found the U-GH excretion in High RR CNLD infants (2,393 ± 3,072) was not significantly different from the paired study night in air/usual supplemental $O_2$ (1,932 ± 2,209; $P = 0.71$). The mean U-GH excretions in higher inspired $O_2$ for the Normal RR CNLD infants (306 ± 198; $P = 0.50$) and controls (379 ± 196; $P = 0.41$) were not significantly different from the paired study in air/usual inspired $O_2$. Furthermore, the SEM for the 23 subjects four U-GH samples averaged ±34% of their individual mean on night #1 and ±31% of their individual mean on night #2. The mean U-GH did not differ between the three groups in middle infancy ($P = 0.956$; Fig. 2) and did not correlate with SWS% or SWS mean epoch duration on any of the study nights.

Because of dropout of patients from the High RR CNLD group, we further analyzed the U-GH, RR, and polysomnography variables for the four High RR CNLD infants who had measures in early and middle infancy. This confirmed a statistically significant higher U-GH excretion in the High RR CNLD group (Fig. 2), a similar drop in mean (SD) RR (49.2 [3.9] vs. 31.3 [3.8] vs. 29.6 [6.9]; ANOVA: $P < 0.001$), and evidence of improved sleep quality (sleep efficiency and REM arousal index) after the tachypnea had resolved (Tables 1, 2). The improvement in sleep quality for the High RR CNLD infants contrasts that demonstrated for the seven Normal RR CNLD infants who had better sleep quality which was sustained from early infancy. For the five controls who had paired studies in early and middle infancy, there were no significant differences in U-GH (Fig. 2), RR (27.4 [5.8] vs. 27.6 [8.4]; $P =$ NS), or polysomnographic variables.

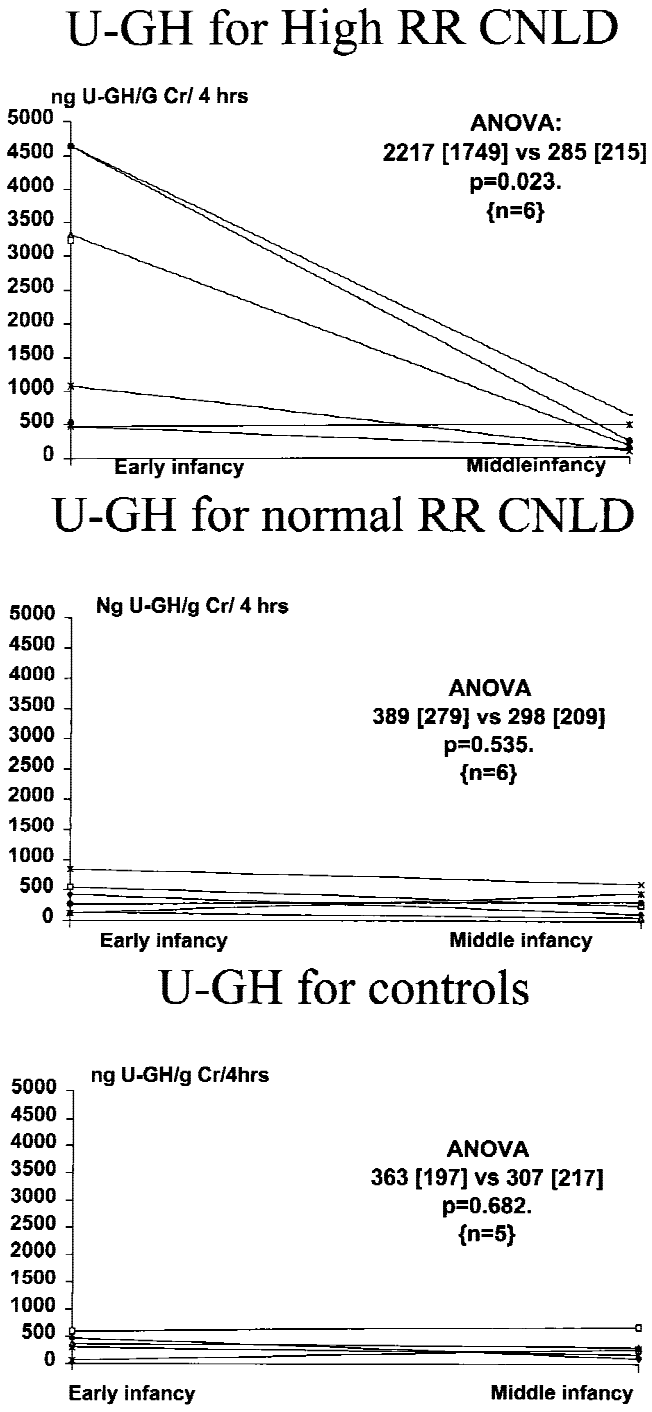


**Fig. 2. The values of mean U-GH excretion for infants with paired studies in early and middle infancy. Mean (SD) for each group is listed.**

## DISCUSSION

This study has shown elevated U-GH in tachypneic CNLD infants at 1 month mean corrected age of the order seen in ''stressed'' term infant in the first days of life. The U-GH results are lower for healthy preterm infants and CNLD infants with a normal respiratory rate than for the healthy preterm infants of Quattrain et al.[32] and is consistent with a reduction in GH during the first weeks of life in well preterm infants.[28,32] Interestingly, U-GH excretion for Normal RR CNLD and control infants did not change significantly through infancy and remained higher than has been documented in other studies of U-GH in young children, postpubertal adolescents, and adults in whom reported mean U-GH levels (ng/g Cr) were <50 ng GH/g Cr.[30,33–38] In the present study, U-GH levels in High RR CNLD infants fell at the same time as sleeping respiratory rates ''normalized'' by 6 months.

We have three possible explanations for our U-GH findings. The most likely explanation is that elevated U-GH reflects a nonspecific elevation of serum GH as a ''stress hormone'' response.[39] Increased caloric demands may lead to increased catecholamine release, leading in turn to hypermetabolism[2,3,11] and augmented GH release.[39] Theoretically, use of exogenous glucocorticoids could augment this process. All High RR CNLD infants, 5/7 of the Normal RR CNLD infants, and 1/7 controls (for vocal cord granulomas) received courses of systemic dexamethasone. Thus, exogenous corticosteroids are unlikely to be the sole explanation for the differing U-GH excretion between groups. Persistent hypersecretion of GH has been reported in four of five ''stressed,'' growth retarded (birthweight <10%), preterm infants (two of whom had CNLD) until a term equivalent age.[19] While two of four growth retarded infants were in the tachypneic CNLD group, the other two were in the nontachypneic CNLD group. If a ''stress'' response to the severity of lung disease were the predominant mechanism, it would be reasonable to expect a fall in GH levels (half-life of approximately 19 min)[39] in tachypneic CNLD infants with the initiation of higher inspired $O_2$, which did not occur. However, the ''stress'' response may be mediated by other hormonal factors, which may take longer to respond.

A second possibility is GH resistance, as demonstrated in malnourished infants[12] and patients with anorexia nervosa.[40] Malnutrition is associated with elevated serum GH and reduced serum insulin-like growth factor type 1 (IGF-1).[12] Measurement of serum IGF-1 would have been useful in our study, although parallel patterns of U-GH and IGF-1 excretion in preterm and term infants have recently been reported.[32] Nonetheless, all study infants were managed at home during infancy and none were cachectic, making GH resistance a less likely explanation.

A third explanation is that elevated U-GH and, thus, serum GH[19–22] may reflect a feedback loop involving a direct effect of GH on lung repair and growth. Evidence for this possibility is suggested by the demonstration of increased lung growth in subjects with acromegaly.[41] Recently, Donnelly et al.[42] speculated that increased lung growth in nonsmoking acromegalics was attributable to increased alveolar number rather than increased alveolar size. Previously, Armour et al.[43] had suggested that swimmers with greater lung volumes than elite runners and controls might have obtained their superior lung function on the basis of an increased alveolar number, rather than an increase in alveolar size. The postulated mechanism of increased alveolar multiplication occurring during adolescence in adult elite swimmers involved a periodic hypoxic stimulus (swimming) as a cause for elevated serum GH levels.[43] Earlier, an association between exercise during hypoxia and increased serum GH had been described.[44,45] Thus, intermittent hypoxic stimuli may stimulate GH release, which in turn facilitates the release of an undetermined insulin-like-growth factor prompting alveolar multiplication and improved gas exchange. Infants with CNLD and acceptable baseline $SaO_2$ (>93%) are susceptible to repeated episodes of arterial $O_2$ desaturation when feeding and during REM sleep.[23,46] Improved gas exchange would correlate with less frequent $O_2$ desaturation and ''normalization'' of the respiratory rate seen in High RR CNLD infants by mid-infancy. Thus, the marked elevation of U-GH in tachypneic CNLD infants may represent a biological mechanism mediating lung repair and growth in response to intermittent hypoxemia.

There are limitations when interpreting U-GH data because of the interindividual and intraindividual variations in U-GH assays.[30,38,47] This limitation of U-GH assays is important when attempting to make a definitive diagnosis of GH deficiency in an individual, although it is less relevant when describing trends of GH production.[30] With repeated nightly samples over periods of 4 hr (approximately two sleep cycles in young infants[27,48]), we attempted to minimize this problem as has been suggested in older children.[22] The variability in U-GH excretion during the course of the night for all groups during the paired studies in early infancy (the standard error was 31–34% of the individual patient's mean U-GH sample per night) was of the order reported previously.[37,38,47]

This study has also provided the first longitudinal data for sleep architecture variables in CNLD infants using overnight polysomnography. Similarities exist between the REM sleep findings for CNLD infants in the present study and the two reported cross-sectional studies of sleep architecture in infants with CNLD.[18,49] In the present study, CNLD infants demonstrated unchanged REM%, which comprised fewer epochs of increasing duration during infancy. This coincided with a decrease in the REM arousal index, improved sleep efficiency, and a similar total sleep time. By mid-infancy, CNLD infants with an $SaO_2 \geqslant 93\%$ have achieved similar sleep architecture to that demonstrated in term infants.[49] For tachypneic infants with CNLD, sleep consolidation coincided with improved respiratory function.[7] Consequently, this study demonstrated that more severe lung disease, as reflected by persisting tachypnea in sleep, is associated with higher U-GH, slower growth, and more disrupted sleep architecture in early infancy.

## Implications for Clinical Management

### Weaning Supplemental Oxygen

Use of accessory muscles of respiration (''work of breathing''), the presence of pulmonary hypertension, neurodevelopmental progress, and growth parameters

need to be considered in relation to the maintenance of an adequate $SaO_2$. A sleeping frequency below 45 breaths/min before 3 months corrected age suggests less severe lung disease. Consequently, an arbitrary guide to adequate $SaO_2$ in CNLD would include maintaining the mean sleeping $SaO_2$ >93% and keeping an $SaO_2$ ⩾90% for at least 90% of sleep time.

### Lung Repair and Growth

We speculate that exogenous GH could be used to stimulate alveolar growth in infants with more severe lung disease. Given that sufficient calories are provided, the anabolic effect of GH would stimulate somatic growth and lung growth. This could improve gas exchange, protect against intermittent hypoxemia during sleep, and hasten weaning from supplemental $O_2$.

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## APPENDIX

### Definitions

*Apnea:* Cessation of breathing for three missed respiratory cycles (i.e., >5 sec). Obstructive, central, and mixed (combination of central and obstructive components) apnea are recognized.

*Arousal:* Alteration in an EEG-defined sleep state which may correspond with an obvious body movement.

*Arousal index:* Number of arousals per hour of sleep state (e.g., REM arousal index).

*Chronic neonatal lung disease* (CNLD): Oxygen dependency beyond 36 weeks postconceptional age in preterm infants born ⩽30 weeks gestation.

*Epoch:* Period in an EEG- and EOG-defined sleep state (e.g., REM epoch).

*NREM sleep:* Non-rapid eye movement sleep is characterized by high voltage, low frequency EEG waveforms, absent body movements, absent rapid eye movements, the maintenance of body tone with regular cardiac and respiratory rates.

*Obstructive apnea:* A respiratory effort characterized by the absence of nasal airflow for >5 sec with increased abdominal, diaphragmatic, thoracic, and submental muscular effort as reflected in EMG traces. Paradoxical abdominal and thoracic movements may occur.

*REM sleep:* Rapid eye movement sleep. A stage of sleep characterized by behavioral activity, decreased resting muscle activity, reduced pharyngeal muscle tone, and irregular respirations. The characteristic occurrence of REM on the EOG leads facilitates recognition of this sleep state.

*Sleep efficiency:* The proportion (%) of time spent asleep following sleep onset (not lights out) and prior to awakening at the end of the study ((Sleep time–awake time) /sleep time × 100).

*Sleep time:* Time spent asleep between sleep onset and awakening prior to terminating the study.

*Slow wave sleep:* A subset of NREM sleep, characterized by behavioral quiescence, regular respirations, and the absence of body and eye movements.

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