Effect of Phototherapy on Cardiorespiratory Activity during Sleep in Neonates with Physiologic Jaundice

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Abstract

Background: Phototherapy is considered the standard of care for neonatal jaundice. However, its short-term cardiorespiratory effects have not been studied thoroughly.

Objectives: To assess the cardiorespiratory effect of phototherapy during sleep in term infants with physiologic jaundice.

Methods: We performed two polysomnography studies during 3 hours sleep in 10 healthy term infants with physiologic jaundice; each infant served as his/her own control. The first study was performed just prior to phototherapy and the second study during phototherapy 24 hours later. Heart and respiratory rates, type and duration of apneas, and arterial oxygen saturation were analyzed during active and quiet sleep.

Results: Term infants (gestational age 38.6 ± 1.4 weeks, birth weight 3.2 ± 0.5 kg) underwent the two polysomnography studies within a short time interval and had a comparable bilirubin level (3.6 ± 0.8 and 4.5 ± 0.8 days; 14.5 ± 1.4 and 13.8 ± 2.1 mg/dl, *P* = NS, respectively). There was no difference in sleeping time or the fraction of active and quiet sleep before or during phototherapy. During active sleep under phototherapy there was a significant decrease in respiratory rate and increase in heart rate (54.3 ± 10.3 vs. 49.1 ± 10.8 breaths/minute, and 125.9 ± 11.7 vs. 129.7 ± 15.3 beats/minute, respectively, $P < 0.05$), as well as a decrease in respiratory effort in response to apnea. These effects were not found during quiet sleep. Phototherapy had no significant effect on oxygen saturation, apnea rate or periodic breathing in either sleep state. No clinical significant apnea or bradycardia occurred.

Conclusions: Phototherapy affected the cardiorespiratory activity during active sleep but not during quiet sleep in term infants with physiologic jaundice. These effects do not seem to have clinical significance in "real-life" conditions.

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Neonatal jaundice is common in the newborn nursery and phototherapy is considered the standard of care when treatment is indicated [1]. Phototherapy is an efficient therapy and is considered to be safe, although several side effects have been described [1–5]. These include physiologic and behavioral effects on most of the organ systems of the newborn infant.

Altered balance between the different sleep stages and decrease in the overall sleep time [3], and disturbance of the circadian rhythm for a few days during and after phototherapy have been reported [2]. Biochemical factors that might affect sleep include a decrease in the level of tryptophan, a precursor of the neurotransmitter serotonin during phototherapy [4]. Endocrine effects such as reduction of increased levels of growth hormone during jaundice [5], or effects on melatonin secretion might affect sleep. It was reported that melatonin is secreted already in the first 72 hours of life without circadian pattern [6], and that there was an increase in melatonin level in response to light deprivation imposed by covered eyes during phototherapy [7]. While this is circumstantial evidence on possible effects on sleep pattern during phototherapy, direct information on the cardiorespiratory activity is limited and derives from relatively old studies [8–10].

Previous studies reported increased peripheral circulation, transient decrease in systolic blood pressure and increase in heart and respiratory rate during phototherapy [8]. Several investigators found an increase in respiratory rate during phototherapy while in active and quiet sleep, whereas others found this increase to be more significant during quiet sleep [9,10]. While it seems that phototherapy does affect cardiorespiratory activity, several issues are still not verified. What is the magnitude and significance of these changes? Is it the effect of phototherapy, of hyperbilirubinemia or of the cause of jaundice (previous studies were done at different levels of bilirubin with variable etiologies of jaundice).

The aim of the present study was to investigate the effects of phototherapy on cardiorespiratory activity during the different sleep states. Thus, we performed polysomnography before and during phototherapy in healthy infants with physiologic jaundice at a comparable bilirubin level and age. Our hypothesis was that phototherapy will be associated with cardiorespiratory changes, particularly increased heart and respiratory rate, shallow breathing and increased apnea rate. We also hypothesized that these differences will be related to sleep state, but without clinical consequences.

Patients and Methods

The study group included 10 healthy term infants with physiologic jaundice born at the Bnai Zion Medical Center, Haifa, Israel. The infants were chosen sequentially according to the following inclusion criteria: normal pregnancy and delivery, Apgar score >8 at 1 and 5 minutes, term (>37 weeks gestational age), birth weight 2.5–4 kg, and parental informed consent. All the mothers were healthy and none had taken any medication, drug or alcohol or had smoked during pregnancy. There was no history of neurologic, cardiac, respiratory or metabolic disease in the family. Physiologic jaundice was considered jaundice in a term healthy infant with no hemolysis or G6PD deficiency.

All infants had a normal physical examination by a senior neonatologist who approved their participation prior to the study. Excluded from the study were infants at risk of sepsis, hemolysis, dehydration, anemia or any other sign of disease that would not conform to the definition of physiologic jaundice in a healthy term infant. The study was conducted at the Bnai Zion Medical Center, Haifa, Israel. Both Ethics Committees of the Medical Center and the Israel Ministry of Health approved the study. Written informed consent was obtained from the parents of the participating infants.

Each infant underwent two polysomnography studies and served as his/her own control. The two studies were performed in an incubator 24 hours apart, immediately prior to and under phototherapy, as in "real life" routine. The first study was always the one without phototherapy because of the ethical limitation that phototherapy could not be withheld for study purposes in infants who needed it for patient care. The studies were performed during sleep in a supine position 30 minutes after the babies were fed.

A minimum of 3 hours sleep study (polysomnography, 14 channels, Nihon Kohden, Japan) was conducted in the Apnea Investigation Laboratory at the Bnai Zion Medical Center, which is adjacent to the nursery and the obstetric ward. The lab is isolated from external environmental stimuli, such as noise, light and significant temperature changes. All studies were performed at late evening hours. The studies included electroencephalography (C1-A2, C3-A4), Electro-oculography, abdominal and chest movements (Pisoelectric Electrode, Technion, Haifa, Israel), nasal air capnography (Datex, Finland), and arterial oxygen saturation (Pulse oximeter, Nellcor N-100, CA, USA). The pulse oximeter sensor was covered to protect it from the phototherapy light. Signals were recorded at a paper speed of 5 mm/second. The recorded signals were continuously analyzed and averaged. Events of apnea and desaturation were analyzed separately. Thermal environmental temperature was continuously monitored and set at the appropriate range for term infants according to age (29.8–32.8°C.). Infant temperature was measured routinely. The researchers who analyzed the data were unaware of the phase of the study (with or without phototherapy).

The following data were derived: heart and respiratory rates (analyzed automatically by spectral analysis), oxygen saturation, number of apneas (longer than 3 seconds), their type (central vs. obstructive), their duration and associated heart rate. Periods of arousal or intermediate sleep states were excluded from the analysis. Sleep state (active or quiet sleep) as well as arousals were defined using established criteria [11,12]. The proportion of active and quiet sleep was computed from the total analyzable sleep time, excluding arousals determined by the laboratory technician and the sleep records and transitional/intermediate states. Epochs of 30 seconds were used for sleep record analysis and staging. Two researchers reviewed the records to ascertain reliability of sleep staging. Apnea was defined as cessation (at least 90% flattening of the signal of breathing) of nasal flow for 3 seconds. Periodic breathing was defined as three or more central apneas lasting more than 3 seconds interrupted by respiration lasting 20 seconds or less [13]. Apnea-associated breath depth was derived from the ratio of the mean breath amplitude of the 5 seconds preceding and following every apnea episode. Sleep efficiency was defined by subtracting "total interruption time" from the "total sleep time" divided by the "total sleep time." All data were standardized for sleep time in minutes.

Statistical analysis

Paired *t*-test was used for continuous variables with normal distribution. A significant statistical difference was defined $P < 0.05$. The data are presented as mean ± standard deviation.

Results

The study population consisted of 10 infants; their gestational age was 38.6 ± 1.4 weeks and birth weight 3203 ± 547 g. The study before and the study during phototherapy were performed at a comparable age (3.6 ± 0.8 vs. 4.5 ± 0.8 days, P = NS) and bilirubin level (14.5 ± 1.4 vs. 13.8 ± 2.1 mg/dl, P = NS).

There was no significant difference in sleep efficiency, time spent asleep out of the total sleep study, and the proportion of active or quiet sleep with and without phototherapy [Table 1]. Respiratory rate was lower and heart rate faster under phototherapy during active sleep [Table 2]. Cardiorespiratory activity during apnea while in active sleep was comparable with and without phototherapy. The mean ratio of breath depth before and after apnea increased significantly during phototherapy in active sleep [Table 3]. In contrast, no significant changes during phototherapy were noted in quiet sleep [Tables 2 and 3]. When analyzing only those infants who had apneas in and out

Table 1. Sleep state with and without phototherapy

	No phototherapy	Phototherapy	*P*
Active sleep (min)			
Duration (min)	41.5 ± 3.7	39.8 ± 5.9	NS
Relative time	0.50 ± 0.07	0.49 ± 0.13	NS
Quiet sleep (min)			
Duration (min)	35.1 ± 2.3	38.8 ± 3.2	NS
Relative time	0.46 ± 0.07	0.50 ± 0.10	NS

Table 2. Cardiorespiratory activity during sleep

	No phototherapy	Phototherapy	*P*
Active sleep			
Respiratory rate*	54.3 ± 10.3	49.1 ± 10.8	<0.05
Heart rate**	125.9 ± 11.7	129.7 ± 15.3	<0.05
Oxygen saturation (%)	96.6 ± 1.7	97.3 ± 1.3	NS
Quiet sleep			
Respiratory rate*	46.0 ± 9.9	45.7 ± 12.0	NS
Heart rate**	123.1 ± 12.5	127.7 ± 14.4	NS
Oxygen saturation (%)	97.0 ± 1.7	97.7 ± 1.5	NS

* Breaths per minute

** Heart beats per minute

of phototherapy (n=6), there was a trend towards increase in central apnea duration while under phototherapy ($P = 0.07$), and increased heart rate under phototherapy as compared to no phototherapy ($P < 0.02$). There was no significant difference in the number or duration of events of periodic breathing in the different sleep states before or during phototherapy [Table 4].

In summary, the effects of phototherapy on cardiorespiratory activity during active sleep included a decrease in respiratory rate and increase in heart rate as well as an increase in breath-depth ratio (representing decreased effort of breathing) after apnea. In quiet sleep no significant effects were detected.

Discussion

Our study found that phototherapy in "real-life" conditions affects the cardiorespiratory activity during active sleep but not during quiet sleep. Sleeping time and sleep state (active or quiet sleep) were not affected. No significant effects were detected on oxygen saturation, apnea rate or periodic breathing.

Table 3. Cardiorespiratory activity during sleep apnea

	No phototherapy	Phototherapy	*P*
Active sleep			
Apnea number (per min)	0.28 ± 0.14	0.22 ± 0.18	NS
Central apnea (per min)	0.27 ± 0.14	0.22 ± 0.18	NS
Obstructive apnea (per min)	0.02 ± 0.008	0.03 ± 0.008	NS
Apnea with no prior movement	0.23 ± 0.13	0.17 ± 0.15	NS
Apnea with prior movement	0.04 ± 0.04	0.035 ± 0.04	NS
Duration of apnea (sec)	5.5 ± 1.0	5.0 ± 1.0	NS
Heart rate during apnea	132 ± 11	137 ± 12	NS
SpO_2 (%)	95.9 ± 1.9	96.8 ± 1.9	NS
Breaths ratio before/after apnea*	1.08 ± 0.16	0.97 ± 0.21	NS
Breath depth before/after apnea*	1.1 ± 0.2	1.3 ± 0.3	0.02
Quiet sleep			
Apnea number (per min)	0.09 ± 0.04	0.07 ± 0.02	NS
Central apnea (per min)	0.15 ± 0.12	0.09 ± 0.06	NS
Obstructive apnea (per min)	0.02 ± 0.008	–	NS
Apnea with no prior movement	0.13 ± 0.12	0.07 ± 0.04	NS
Apnea with prior movement	0.01 ± 0.01	0.01 ± 0.02	NS
Duration of apnea (sec)	5.7 ± 0.4	5.9 ± 1.2	NS
Heart rate during apnea	126.7 ± 3.9	127.9 ± 4.2	NS
SpO_2 (%)	95.8 ± 0.5	96.8 ± 0.7	NS
Breaths ratio before/after apnea*	1.05 ± 0.04	1.02 ± 0.04	NS
Breath depth before/after apnea*	0.9 ± 0.11	1.08 ± 0.1	NS

* Ratio between the 5 seconds preceding and following every apnea episode

Table 4. Periodic breathing during sleep

	No phototherapy	Phototherapy	*P*
Active sleep			
Periodic breathing events	1.6 ± 0.6	1.1 ± 0.6	NS
Duration of periodic breathing (sec)	18.3 ± 6.0	20.5 ± 6.0	NS
Quiet sleep			
Periodic breathing events	1.3 ± 0.7	0.3 ± 0.2	NS
Duration of periodic breathing (sec)	22.8 ± 8.3	28.2 ± 13.8	NS

Phototherapy is the standard care for neonatal jaundice that requires therapy. When phototherapy is needed the infants are usually placed almost naked in the incubator with their eyes covered for protection. The procedure used in the present study, adhering to the real clinical conditions, could detect the cardiorespiratory effects of phototherapy as used in the neonatal unit. Both studies were performed at comparable bilirubin levels and age, hence the effects of the jaundice and maturational changes of the autonomic and cardiorespiratory systems were accounted for. All infants had "physiologic" jaundice. A search of the literature revealed two previous relatively old polysomnography studies that examined the effects of phototherapy. The first was done in infants without jaundice [9] and the second in infants with different levels of bilirubin and jaundice from variable etiologies, and in that study almost half the participants underwent exchange transfusion [10]. Thus, our study is the first to perform a polysomnography to evaluate cardiorespiratory activity in the different sleep states during phototherapy for physiologic jaundice.

In our study we did not find a significant effect of phototherapy on sleep state and sleep efficiency. Previous data were not consistent, and while a longer study reported an increase in all sleep states [10], others reported a decrease in the daily sleep time and imbalance between the different sleep states under phototherapy [3]. Sleep interruptions were not analyzed in the present study. However, sleep efficiency was not affected by phototherapy.

We observed an increase in heart rate during active sleep but not during quiet sleep under phototherapy. A previous study reported an increase in heart rate and decrease in systolic blood pressure (that returns to baseline within 8 hours) during phototherapy [8]. This could result from decreased peripheral vascular tone due to the light effect or because of increased peripheral temperature (without increase in core temperature) under phototherapy, and compensatory increased heart rate. Increased skin blood flow during phototherapy resulting from cutaneous vasodilatation was shown by laser Doppler flowmetry [14]. Others reported on ductus arteriosus reopening with no hemodynamic significance in preterm infants during phototherapy [15]. Benders et al. [16] noted a transient decrease in left ventricular output, an increase in left pulmonary artery blood flow, an increase in cerebral blood flow velocity, and a decrease in renal blood flow velocity in term infants under phototherapy. All changes disappeared after termination of phototherapy [16]. Walther and co-workers [17] showed decreased cardiac output (6%), reduced stroke volume, and increased skin flow (41%) during phototherapy. Other studies reported on phototherapy-associated attenuation of postprandial increase of mesenteric blood flow in term and preterm infants [18].

We also observed a decrease in respiratory rate during active sleep but not during quiet sleep, while oxygen saturation remained stable under phototherapy throughout the study in both sleep states. Other investigators found an increase in respiratory rate, which was more significant during quiet sleep [8–10]. Von Bernuth and Janssen [9] evaluated the effect of phototherapy in

term infants with no hyperbilirubinemia, in a crib, at a mean age of 6 days with a partial polygraphic study. Body temperature increased by 0.45°C under phototherapy, and respiratory rate increased in both active and quiet sleep. Korinthenberg and team [10] performed polysomnography to evaluate the effect of phototherapy at different ages, different bilirubin levels and in infants with different etiologies of jaundice, of whom almost half underwent exchange transfusion. They also demonstrated an increase in respiratory rate during phototherapy in jaundiced newborns, which was more significant during quiet sleep. Another interesting finding in this study was a negative correlation between serum bilirubin and respiratory rate during quiet sleep. This effect was diminished while in active sleep. Oh and Karecki [19] found a significantly higher rate of breathing and insensible water loss in term infants during phototherapy than in normal controls and in jaundiced infants not receiving phototherapy. Infants in the control group had slightly lower rectal temperature than those receiving phototherapy [19]. Kjartansson and associates [20] did not find significant differences in oxygen consumption or respiratory water loss after one hour of phototherapy under rigorous control of ambient conditions with absence of heat stress. Fok et al. [21] did not find that phototherapy had a significant effect on oxygen consumption, resting energy expenditure, heart rate, respiratory rate or rectal temperature in 202 thermally controlled and stable term and preterm infants. In their study, sleep and activity state were not defined and subtle changes could have been missed. The limitation of our study, which was conducted in "real-life" conditions, was that we monitored the environmental temperature but did not have continuous monitoring of core temperature before and during phototherapy. Our study group was relatively small, yet the number of events recorded and analyzed allowed us to gain significant information from our data. It is possible that some cardiorespiratory changes could have been missed (type b error), but these were probably of minimal clinical significance. Differences between the studies' methodology, no uniform attention to sleep or activity state, and inclusion of infants with jaundice of different etiologies and different levels could account for the inconsistency between studies. Although the cardiorespiratory effects of phototherapy observed during active sleep in our study were statistically significant, they do not appear to have clinical significance.

No significant effects were detected in apnea rate or periodic breathing during phototherapy in our study. Although the effect of phototherapy on the physiologic response to apnea was minor [Table 3], we observed that the recovery of breath depth following apnea was significantly decreased in active sleep only. Other investigators found that in quiet sleep, end-expiratory obstruction caused increased depth of breath, increased inspiratory time and decreased respiratory rate that was not seen during active sleep [22,23]. Thus, not only is the response to apnea blunted in active sleep, during phototherapy it is even decreased. Nevertheless, oxygen saturation as well as respiratory rate remained stable in our study. The central organization of respiratory control during the two sleep states is different. While in quiet sleep respiration is affected by metabolic parameters mediated by automatic ponto-medullary centers, in active sleep the irregular respiratory pattern is controlled by higher voluntary, yet unknown, centers. These are probably more independent of well-known metabolic and vagal reflexes [10]. Phototherapy might affect the control of breathing through temperature, biochemical and metabolic factors mediated by the autonomic system [2,24]. Our infants were relatively stable.

The cardiorespiratory effects of phototherapy were minor and were observed during active sleep but not during quiet sleep. Although the effect of sleep state appears to be dominant in our study, it should be noted that it became significant only under phototherapy. Active sleep is a more vulnerable sleep state in the newborn infant. During active sleep there is inhibition of the intercostal muscles, rib cage distortion, decreased functional residual capacity, increased respiratory rate, increase in diaphragmatic work of breathing, and decrease in transcutaneous arterial oxygen pressure. Active sleep was also associated with a slower and weaker response to nasal obstruction, increased rate of apnea of short duration (<10 sec), and increased vulnerability to factors inducing apnea or periodic breathing such as hyperthermia. Infants during active sleep are at greater risk for oxygen desaturation during apnea, and there is a decreased response to hypoxia and hypercapnia [25]. We observed in active sleep as compared to quiet sleep an increase in heart rate, breathing rate, number of apneas and increase in central apneas and periodic breathing. Only active sleep was affected by phototherapy. This conceivably reflects a decrease in autonomic control and compensatory mechanisms during active sleep further affected under phototherapy. The exact nature of this possible strain has not yet been elucidated. Although the effects were of statistical significance they do not seem to have clinical significance since no prolonged apnea, bradycardia or desaturation was observed.

We conclude that phototherapy affects cardiorespiratory activity during active sleep and not during quiet sleep in term infants with physiologic jaundice. These effects do not have clinical implication in "real-life" conditions.

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