

Influence of Thermal Drive on Central Sleep Apnea in the Preterm Neonate

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Background: The incidence of apnea in neonates depends on a number of factors, including sleep state and thermoregulation.

Objective: To assess the role of thermal drive (body heat loss [BHL]) in the mechanisms underlying short episodes of central apnea during active and quiet sleep in neonates.

Material and Method: Twenty-two neonates (postconceptional age: 36.3 ± 0.9 weeks) were exposed at thermoneutral (incubator temperature: 32.5°C), warm (34.2°C), and cool (30.4°C) conditions during 3 consecutive morning naps. Oxygen consumption ($\dot{V}\text{O}_2$), skin and rectal temperatures, and central apnea were scored during active sleep and quiet sleep. The thermal drive was expressed as BHL calculated using indirect partitioned calorimetry.

Results: As expected, apnea occurred more frequently in active sleep than in quiet sleep ($P < 0.001$). The frequency of apnea in active sleep was higher in the warm condition ($P < 0.05$). In contrast, apnea episodes

were less frequent ($P < 0.05$) and shorter ($P < 0.05$) for cool exposure, during which $\dot{V}\text{O}_2$ and rectal temperature increased. The frequency ($P < 0.001$, $r^2 = 0.31$), mean ($P < 0.05$, $r^2 = 0.06$), and maximum ($P < 0.001$, $r^2 = 0.19$) durations of apnea were correlated with the BHL: the greater the BHL (body cooling), the less frequent and the shorter the apnea episodes. In contrast, no relationship between apnea and mean skin or rectal temperature was observed.

Conclusion: Apneic events were more closely related to BHL than to body temperatures. In cool exposure, the decreases in the duration and frequency of apneic episodes suggest that these events depend on the metabolic drive (which is proportional to energy expenditure).

Keywords: apnea, neonate, temperature, sleep, metabolism

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IN NEONATES, THE INCIDENCE OF APNEA DEPENDS ON A VARIETY OF FACTORS, SUCH AS BIRTH WEIGHT,¹ SEX,² GESTATIONAL AGE,³ AND POSTNATAL AGE.^{3,4} Central apnea is generally reported as occurring more frequently during active sleep than during quiet sleep.^{2,3,5-7} Many authors have pointed out that apnea incidence is also closely related to ambient temperature in both full-term⁸⁻¹⁰ and preterm neonates^{9,11,12} and that the rate of apneic events is increased by warm exposure (i.e., thermal drive). Although preterm neonates are more often exposed to cool stress than to warm stress, little is known about the influence of cool exposure on the incidence of apnea in the different sleep states. Bader et al¹¹ reported a lower rate of central apnea during transient decreases in incubator temperature from warm (29°C) to thermoneutral conditions (24°C) over 30 minutes, although this was only seen during quiet sleep for preterm infants and during active sleep for term infants.

The mechanism linking thermal stress and apnea is unknown and thus warrants further investigation. On the basis of the above-cited studies, it can be supposed that suprapontine influences modify respiratory control, which must be considered as a multiple-interaction system. Abnormal functional interac-

tion among the respiratory system, thermoregulatory system, and sleep processes may alter compensatory responses to autonomic cardiovascular or respiratory challenge and increase the likelihood of life-threatening events later in life.¹³

The effect of thermal stress is usually assessed by monitoring the body's internal temperature (generally esophageal or rectal temperatures, which supposedly represent the core temperature) and/or mean skin temperature.¹⁴ However, the central controller of the thermoregulatory system receives thermal inputs from thermosensitive structures distributed throughout the body. The regulated variable therefore results from a weighted sum of different body temperatures.¹⁵ Hence, to fully understand the thermal influence on apnea incidence in cool environments, it is essential to quantify the magnitude of body cooling that is proportional to the radiant, convective, conductive, and evaporative heat losses (i.e., body heat loss) on the other. Any failure to maintain thermal balance stimulates the body's thermal control mechanisms and thus triggers regulatory adjustments. This approach may help clarify a hypothesis raised by Perlstein et al,⁹ whereby apnea is not specifically induced by changes in air temperature but, rather, through processes controlling the overall body heat loss (BHL). Hence, in the present study, the role of thermal drive in the mechanisms underlying the genesis of central apnea in the sleeping neonate was assessed by taking into account BHL during mild warm and cool thermal exposures.

Central apneic events were monitored in a group of 22 near-term neonates. Indeed, there are few published studies on these infants, who are generally considered to be physiologically similar to term infants, even though their central nervous system and breathing control are less mature than those of full-term infants. Moreover, prematurity increases the risk of sudden infant death syndrome. Despite the need to study the basic physiologic processes underlying short apneic events, most studies

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have focused on pathologic apneic events (usually considered as those lasting more than 20 seconds).

MATERIALS AND METHODS

Subjects

Twenty-two preterm neonates (8 males and 14 females, mean \pm SD gestational age: 30.6 ± 2.0 weeks, birth weight: 1.39 ± 0.37 kg) were investigated at 36.2 ± 0.9 weeks of postconceptional age, when the mean body mass was 2.20 ± 0.19 kg. The neonates were healthy and were free from infections and metabolic, neurologic, or cardiorespiratory problems. According to the questionnaires filled out by the mother and examination of their medical files, none of the neonates or their mothers received alcohol, caffeine, or any treatment that could have modified respiratory and thermal parameters.

The protocol was approved by the Picardy Regional Ethics Committee, and written informed consent was obtained from the parents.

Methods

Recordings were performed in the Neonatology Unit at Amiens University Medical Center. The nursery room temperature was monitored and held constant at 22°C to 24°C (relative air humidity: 30%-40%, air velocity ≤ 0.04 m \cdot sec $^{-1}$, natural convection). The supine neonates (wearing a diaper) lay on a mattress made out of plastic foam in a closed, convectively heated incubator (Médipréma® ISIS, Chambray-les-Tours, France).

Incubator and body temperatures

The incubator temperature (T_{inc} , $^{\circ}\text{C}$) was measured with a thermocouple placed 10 cm above the center of the mattress (accuracy $\pm 0.10^{\circ}\text{C}$; model K; Bioblock, Illkirch, France). The mean temperature of the mattress (T_{m} , $^{\circ}\text{C}$) surface was calculated using 5 thermistors located in the middle and the corners of the upper surface of the mattress (accuracy $\pm 0.10^{\circ}\text{C}$; YSI 402; Bioblock). The infants' rectal temperature (T_{re} , $^{\circ}\text{C}$) was monitored with a thermistor probe (accuracy $\pm 0.10^{\circ}\text{C}$; YSI 402; Bioblock) inserted 2 cm beyond the anal sphincter; this core temperature is currently considered to be the major stimulus of the thermoregulatory system. The mean skin temperature (\bar{T}_{sk} , $^{\circ}\text{C}$) was averaged from abdominal and cheek skin temperatures, measured with thermocouples (accuracy $\pm 0.10^{\circ}\text{C}$, model K; Bioblock). Each probe was covered by an aluminum foil patch to reduce the effect of heat radiation from the incubator walls. Body and air temperatures were continuously sampled at 10-second intervals in the morning between 2 meals.

Sleep

Sleep states (active sleep, quiet sleep, and intermediate sleep) were scored according to Curzi-Dascalova and Mirmiran¹⁶ in 30-second periods, on the basis of electroencephalograms and eye movements (monitored by a piezoelectric quartz accelerometer attached to an eyelid). Limb movements (recorded using accelerometers attached to the wrist and ankle) and electrocardiogram

using standard derivations and 3 patch electrodes (1 on each side of the thorax and 1 on the left flank) were also recorded. All recordings were continuously monitored on a polysomnograph (Alice 4, Respironics®, Nantes, France). The breathing rate was assessed by transthoracic impedance using the electrocardiogram patch electrodes, thus avoiding the need for an additional sensor.^{12,17} Oxyhemoglobin saturation was recorded from the transcutaneous pulsed oxygen saturation (SpO_2), which was measured throughout the experiment using a pulse oximeter with a neonatal sensor (Oximax MAX-N, Tyco Healthcare Group LP, Nellcor Puritan Bennett Division, CA) placed on the right hand. Oxygen consumption ($\dot{V}\text{O}_2$, mL \cdot min $^{-1}\cdot$ kg $^{-1}$) was measured (using a mask gently placed on the neonate's face) in the absence of body movements for more than 30 seconds and at least twice during episodes of active sleep and quiet sleep. The O_2 concentration was continuously measured during the test using a mass spectrometer (MGA-1100, GE Marquette Medical Systems, Milwaukee, WI) calibrated with standard gases of known concentrations at the beginning of each experiment. $\dot{V}\text{O}_2$ was converted into standard temperature and pressure, dry units.

Experimental Design

The measurements were performed during 3 successive morning naps (during the period from 09:00 to 12 noon). On the first morning (baseline condition: N), T_{inc} was set to thermoneutrality using a skin-temperature, servo-controlled system designed in our laboratory.¹⁸ This interactive device ensures the maintenance of a thermal condition that takes account of each neonate's particular thermoregulatory requirements. Hence, the thermal environment fulfilled the criteria for thermoneutrality given by Sauer et al.¹⁹

For the second (mild warm condition) and third sessions (mild cool condition), T_{inc} was set to $T_{\text{N}} + 2^{\circ}\text{C}$ and $T_{\text{N}} - 2^{\circ}\text{C}$, respectively. This experimental sequence was chosen in order to rule out a possible effect of thermal adaptation to cool exposure, since the latter can modify thermoregulatory responses and sleep structure.^{20,21} Such a modification has never been reported after warm exposure, which is usually considered to be less disruptive than cool exposure.^{22,23} Only mild thermal influences (similar to those encountered during standard nursing procedures) were considered, in order to avoid over-complex responses.

Data Analysis

Apneic Events

Only central apnea was considered, since its incidence is closely related to the interaction (between breathing control and thermal drive) that we sought to assess. Apnea was recorded using transthoracic impedance and defined as a respiratory pause lasting for longer than 3 seconds, as recommended by Gould et al²⁴; the latter authors emphasized that specific effects of sleep state could be observed for apneic events as short as 2 to 5 seconds. Moreover, this duration facilitates comparisons with data from previous studies using the same criteria.^{8,11,25} We also measured apnea occurring during periodic breathing, since this respiratory pattern is also influenced by thermal drive.²⁵

Apneic episodes were described in terms of their frequency (events·h⁻¹), since the relative durations of active sleep and quiet sleep are known to be influenced by the thermal condition.^{18,21,26} The mean duration (in seconds), 90th percentile duration (in seconds), and maximal duration (in seconds) of the events were also taken into account. Results obtained with the 90th percentile of apnea duration were consistent with those using the maximal duration and, thus, are not presented here.

Body Heat Loss

Neonates lose heat to the environment via several channels.¹⁴ The various heat exchanges (expressed in W) are defined by the following equations (partitional heat loss):

Conductive heat (K) is exchanged between the skin (\bar{T}_{sk} , °C) and the mattress (T_m , °C) surfaces:

$$K = h_k (T_m - \bar{T}_{sk}) A_k A_D$$

h_k = the conductive heat transfer coefficient (= 2 W·m⁻²·°C⁻¹),²⁷

A_k = the percentage of body skin surface area through which heat is flowing (= 0.104),²⁷

A_D = Boyd's body surface area²⁸, m²;

Convective heat is exchanged through air moving over the mucous membrane of the respiratory tract (C_{resp}) or over the skin surface (C):

$$C_{resp} = \dot{V}_E C_p (T_e - T_i) \rho$$

\dot{V}_E = the volumetric respiratory flow (m³·h⁻¹),

C_p = the heat capacity of the air (1.044 kJ·kg⁻¹·°C⁻¹),

$T_e - T_i$ = the temperature difference between expired and inspired air (°C),

The value of T_e is nearly equal to the body's internal temperature,

ρ = volumetric mass of air (kg·m⁻³);

$$C = h_c (T_a - \bar{T}_{sk}) F_{cl} A_c A_D$$

h_c = the convective heat transfer coefficient (W·m⁻²·°C⁻¹) = 2.38 ($\bar{T}_{sk} - T_a$)^{0.25},²⁹ as recommended for natural convection^{29,30},

A_c = the percentage of body surface area available for convective heat exchange (0.804).³¹

The value was determined by taking into account the surface area contacting the mattress (0.104) and the surface area of the upper part of the trunk covered by the diaper (0.092),³¹

F_{cl} = the heat reduction factor due to clothing, which can be calculated as follows³²:

$$F_{cl} = [(h_c + h_r) I_{cl} + 1/f_{cl}]^{-1}$$

h_r = the radiative heat transfer coefficient = 4.7 W·m⁻²·°C⁻¹,^{29,33}

I_{cl} = the effective clothing thermal insulation of the diaper, which ranged from 0.021 to 0.064°C·m²·W⁻¹ according to the actual air temperature measured in each experimental condition.³¹

The clothing surface area factor f_{cl} is 1 + 1.97 I_{cl} ;

Radiant heat exchange (R) is calculated using the Stephan-Boltzmann law:

$$R = h_r A_r [(T_r + 273)^4 - (\bar{T}_{sk} + 273)^4] F_{cl} A_D$$

A_r = the effective radiating area (0.77), determined for a relaxed neonate³⁴ less the percentage of the surface area in contact with the mattress (0.104) and the upper part of the trunk surface area covered by the diaper (0.092), $A_r = 0.574$,

\bar{T}_r = the mean radiant temperature of the environment (°C)²⁹;

Evaporative heat losses occur through the respiratory system (E_{resp}) and through the skin by transepidermal water diffusion (E). The evaporative heat loss due to breathing is related to the volume of expired air (\dot{V}_E , m³·h⁻¹) and the difference in water content between expired (M_e) and inspired (M_i) air (kg·m⁻³):

$$E_{resp} = \dot{V}_E \delta (M_e - M_i)$$

δ = the latent heat of vaporization of water (2.406 kJ·g⁻¹);

$$E = h_e \omega A_c (P_{sH2O} - P_{aH2O}) F_{p,cl} A_D$$

h_e = the evaporative heat transfer coefficient (W·m⁻²·mb⁻¹) = 1.67 h_e ,

ω = the skin wetness (dimensionless) = 0.06,³⁵ since sweating activity is absent or very limited in these preterm neonates,

$P_{sH2O} - P_{aH2O}$ = the water vapor partial pressure difference (mb) between the skin (P_{sH2O}) and air (P_{aH2O}),

$F_{p,cl}$ = the reduction factor for water vapor calculated from the clothing insulation³²:

$$F_{p,cl} = [1 + 2.22 h_c (I_{cl} - (1 - 1/f_{cl})) / (h_c + h_r)]^{-1}$$

By convention, heat loss from the body to the environment is negative. Hence, the BHL (in kJ·h⁻¹·kg⁻¹, 1 W = 3.608 kJ·h⁻¹) to the environment is $-(K + C_{resp} + C + R + E_{resp} + E)$.

The body is a system within which there is inevitably a minimal level of metabolic heat production (M); this balances the heat loss, so that the body heat storage is 0 (i.e., thermoneutral conditions). The BHL can be affected by an increase in metabolic heat production over the minimal rate (due to increased brain activity), such as that encountered in active sleep. The increment (ΔM) limits body cooling and must therefore be added to BHL in order to enable comparisons with quiet sleep.

Statistical Analyses

Effects of thermal conditions and sleep states on temperatures, heart rate, sleep state durations, and oxygen consumption were tested using an analysis of variance (Statview[®] 5.0). When F values were significant (P < 0.05), a Fisher posthoc protected least significant difference test was performed. Data are provided as mean ± SD. Simple linear regressions were computed to correlate the thermal parameters (independent variables) on one hand and apnea frequency, mean duration, and maximal duration (dependent variables) on the other.

RESULTS

The incubator temperature was 32.40°C ± 0.83°C at thermoneutrality, 33.91°C ± 0.74°C for the warm exposure, and 30.31°C ± 0.69°C for the cool exposure. The relative air humidity values were 36.64% ± 8.98%, 34.18% ± 6.93%, and 35.86% ± 8.64% for thermoneutrality, warm and cool thermal conditions, respectively, whereas the corresponding mean radiant temperatures were 25.67°C ± 1.13°C, 27.34°C ± 0.82°C, and 22.70°C ± 1.11°C. The temperature of the mattress surface was 28.12°C ± 1.01°C (thermoneutral), 29.74°C ± 0.73°C (warm), and 25.43°C ± 0.89°C (cool).

Total sleep time during the nap (106 ± 31 min, Table 1) did not depend on the thermal condition ($F_{2,42} = 1.17$, P = 0.32). However, active sleep increased at the expense of quiet sleep (+7.3% and -5.4% of total sleep time, respectively) during cool exposure, when compared with thermoneutrality (interaction thermal condition × sleep state: $F_{2,84} = 2.94$, P = 0.025).

Table 1—Sleep State Expressed as a Percentage of Total Sleep Time in the Different Thermal Conditions

	Thermonutrality	Warm exposure	Cool exposure
Total sleep time, min	112 ± 20	107 ± 39	98 ± 32
Sleep state			
Active	65.4 ± 8.5	66.9 ± 7.1	72.7 ± 12.2 ^{a,b}
Quiet	25.3 ± 6.8	23.5 ± 7.5	19.9 ± 10.0 ^c
Intermediate	9.3 ± 4.9	9.6 ± 5.6	7.4 ± 5.7

Thermal condition × sleep state interaction: $F_{2,84} = 2.94$, $P = 0.025$.

^aCool exposure vs thermonutrality in active sleep: $P = 0.013$

^bCool vs warm exposure in active sleep: $P = 0.049$

^cCool exposure vs thermonutrality in quiet sleep: $P = 0.032$

Heart rate was affected by the thermal load ($F_{2,34} = 3.66$, $P = 0.036$): in contrast with the cool exposure, the warm condition increased heart rate (thermonutral: 146 ± 10 beats·min⁻¹, warm: 151 ± 9 beats·min⁻¹, cool: 146 ± 9 beats·min⁻¹, respectively; warm versus thermonutral or cool: P was always < 0.013).

$\dot{V}O_2$ differed according to the thermal condition ($F_{2,22} = 10.06$, $P < 0.001$): it was higher in the cool condition (thermonutral: 7.25 ± 1.45 vs cool: 9.22 ± 1.46 mL·min⁻¹·kg⁻¹, $P = 0.003$) but was similar in the warm condition and for thermonutrality (thermonutral vs warm: 8.21 ± 1.65 mL·min⁻¹·kg⁻¹, $P = 0.115$). As expected, $\dot{V}O_2$ was larger in active sleep than in quiet sleep (active sleep: 9.18 ± 1.34 vs quiet sleep: 7.28 ± 1.70 mL·min⁻¹·kg⁻¹, $F_{1,11} = 31.84$, $P < 0.001$), whatever the thermal condition (interaction: $F_{2,22} = 0.23$, $P = 0.795$).

Body Temperatures and BHL

Compared with thermonutrality, warm exposure increased the rectal (thermonutral: $37.17^\circ\text{C} \pm 0.25^\circ\text{C}$ vs warm: $37.70^\circ\text{C} \pm 0.07^\circ\text{C}$, $P < 0.001$) and mean skin temperatures (thermonutral: $36.36^\circ\text{C} \pm 0.28^\circ\text{C}$ vs warm $36.70^\circ\text{C} \pm 0.23^\circ\text{C}$, $P < 0.001$). During cool exposure, T_{re} increased (cool: $37.34^\circ\text{C} \pm 0.24^\circ\text{C}$, $P = 0.010$), whereas \bar{T}_{sk} did not change (cool: $36.28^\circ\text{C} \pm 0.37^\circ\text{C}$, $P = 0.151$). The magnitudes of T_{re} and \bar{T}_{sk} were lower in the cool condition than in the warm condition (P was always < 0.030) (Figure 1).

BHL differed according to the thermal condition ($F_{2,24} = 107.86$, $P < 0.001$) and was greater for the cool exposure (-13.79 ± 2.07 kJ·h⁻¹·kg⁻¹) than at thermonutrality or in the warm condition (thermonutral: -11.28 ± 1.84 kJ·h⁻¹·kg⁻¹, warm: -10.59 ± 1.96 kJ·h⁻¹·kg⁻¹, always $P < 0.001$). Furthermore, BHL was lower in active sleep (-10.45 ± 2.87 kJ·h⁻¹·kg⁻¹) than in quiet sleep (-13.33 ± 1.04 kJ·h⁻¹·kg⁻¹, $F_{1,12} = 20.03$, $P < 0.001$).

Apnea

About 4000 apnea episodes were scored. The overall mean apnea frequency was 36.2 ± 32.5 events per hour and the mean event duration was 5.4 ± 1.2 seconds.

In agreement with most literature studies,^{2,3,5-7} the apnea frequency was higher in active sleep than in quiet sleep (47.7 ± 28.6 vs 20.3 ± 23.1 events·h⁻¹, $F_{1,19} = 47.78$, $P < 0.001$, Figure 2), whatever the thermal condition (P was always < 0.024). We

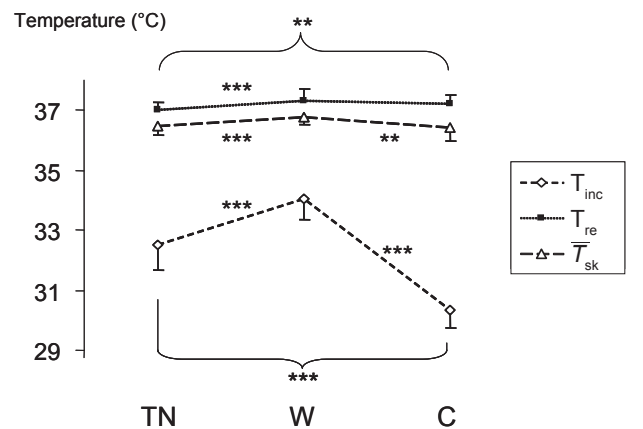


Figure 1—Incubator (T_{inc}), rectal (T_{re}) and mean skin (\bar{T}_{sk}) temperatures ($^\circ\text{C}$) at thermoneutrality (TN) and in warm (W) and cool (C) conditions (mean values ± 1 SD). Posthoc analyses comparing warm exposure, cool exposure, and thermonutrality are indicated: ** $P < 0.01$, *** $P < 0.001$.

observed a significant interaction between thermal load and sleep state ($F_{2,38} = 7.18$, $P = 0.002$); the apnea frequency was lower for cool exposure than at thermonutrality in both active sleep (thermonutral: 45.9 ± 27.2 events·h⁻¹ vs cool: 29.9 ± 22.2 events·h⁻¹, $P = 0.046$) and quiet sleep (thermonutral: 24.2 ± 25.7 events·h⁻¹ vs cool: 13.2 ± 16.6 events·h⁻¹, $P = 0.042$). Warm exposure increased the apnea frequency in active sleep (warm: 67.2 ± 36.4 events·h⁻¹ vs thermonutral: $P = 0.050$), whereas no difference was observed in quiet sleep ($P = 0.388$).

The maximal duration of apneic episodes was shortened by the cool condition (thermonutral: 9.1 ± 2.6 sec, warm: 8.1 ± 1.9 sec, cool: 7.2 ± 1.9 sec, $F_{2,20} = 6.27$, $P = 0.008$; thermonutral vs cool: $P = 0.008$). Active sleep was characterized by a longer maximal duration of apneic episodes (active sleep: 9.1 ± 2.2 sec vs quiet sleep: 7.2 ± 2.1 sec, $F_{1,10} = 13.86$, $P = 0.004$). Thermal and sleep-state effects did not reach a significant level regarding the mean apnea duration (always $F_{2,20} < 1.03$, $P > 0.375$).

Relationship Between Apneic Events and Thermal Influences

The frequency and mean and maximal duration of apneic events were not significantly related to rectal temperatures ($F_{1,94}$ always < 1.83 , $P > 0.179$) or mean skin temperatures ($F_{1,117}$ always < 1.94 , $P > 0.167$). In contrast, the frequency of apneic events was significantly related to BHL ($F_{1,103} = 45.66$, $P < 0.001$, $r^2 = 0.31$, Figure 3): the greater the BHL, the less frequent the apneic events. Likewise, the mean and maximal durations of apneic events were positively correlated with BHL (mean duration: $F_{1,91} = 5.44$, $P = 0.022$, $r^2 = 0.06$; maximal duration: $F_{1,91} = 20.75$, $P < 0.001$, $r^2 = 0.19$). This relationship is consistent with results obtained with $\bar{T}_{sk} - T_{inc}$, although the latter are somewhat less correlated (frequency: $F_{1,117} = 15.84$, $P < 0.001$, $r^2 = 0.12$; mean duration: $F_{1,105} = 2.77$, $P = 0.098$, $r^2 = 0.03$, maximal duration: $F_{1,105} = 9.13$, $P = 0.003$, $r^2 = 0.08$). The correlations with BHL were consistent over the 3 thermal conditions. Moreover, these correlations were significant in both active sleep and quiet sleep (always $F_{1,44} > 5.21$, $P < 0.027$), enabling us to pool the data.

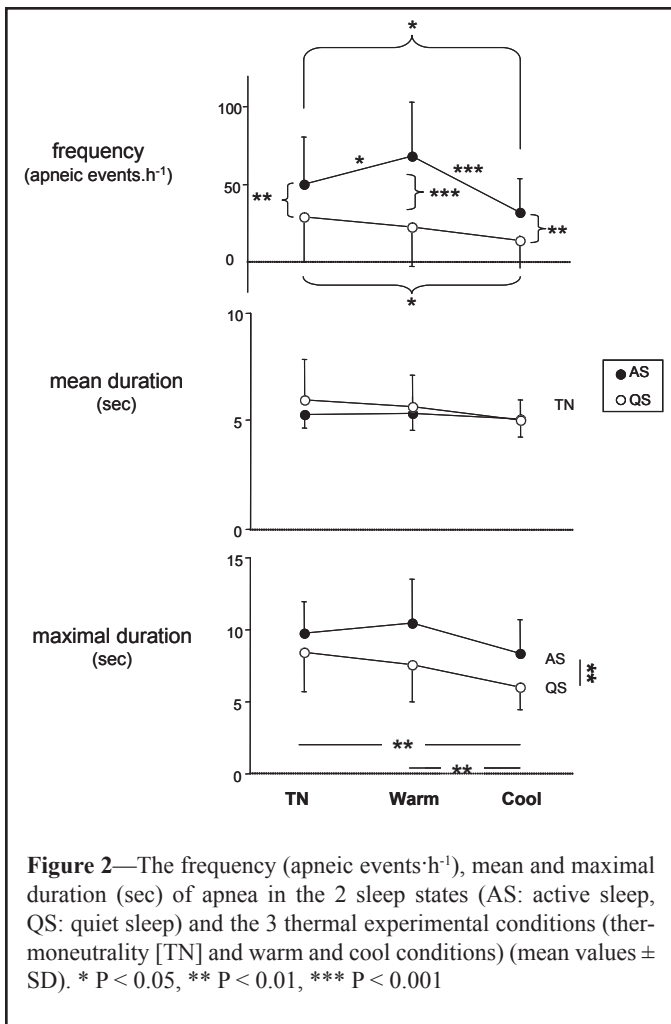


Figure 2—The frequency (apneic events·h⁻¹), mean and maximal duration (sec) of apnea in the 2 sleep states (AS: active sleep, QS: quiet sleep) and the 3 thermal experimental conditions (thermoneutrality [TN] and warm and cool conditions) (mean values ± SD). * P < 0.05, ** P < 0.01, *** P < 0.001

DISCUSSION

The present study indicates that the frequency and the mean and maximum durations of apneic events were significantly related to BHL: the greater the BHL, the less frequent the apneic events and the shorter their mean and maximum durations. These correlations were consistent in both active sleep and quiet sleep and in all 3 thermal conditions.

Thermal, Metabolic, and Hypnic Parameters

Mild thermal challenges (air temperature: +1.5°C and -2.1°C around thermoneutrality) can indeed modify BHL, $\dot{V}O_2$, sleep structure, and heart rate in near-term neonates. This observation can be explained by the fact that their thermoregulatory responses are not very effective, while their body heat exchanges with the environment are large.¹⁴ In response to a mild cool exposure, the thermal responses consist of cutaneous vasoconstriction (a \bar{T}_{sk} decrease), as well as non-shivering thermogenesis, which occurs rapidly (inducing a \bar{T}_{re} increase) via sympathetic activation. These responses (inducing opposite changes in internal and cutaneous temperatures and, thus, increasing the temperature gradient between core and skin) are a normal feature of thermoregulation.¹⁵ Similar findings have been reported by Silverman et al¹⁶ in extremely low-birth-weight neonates. As previously reported in the lit-

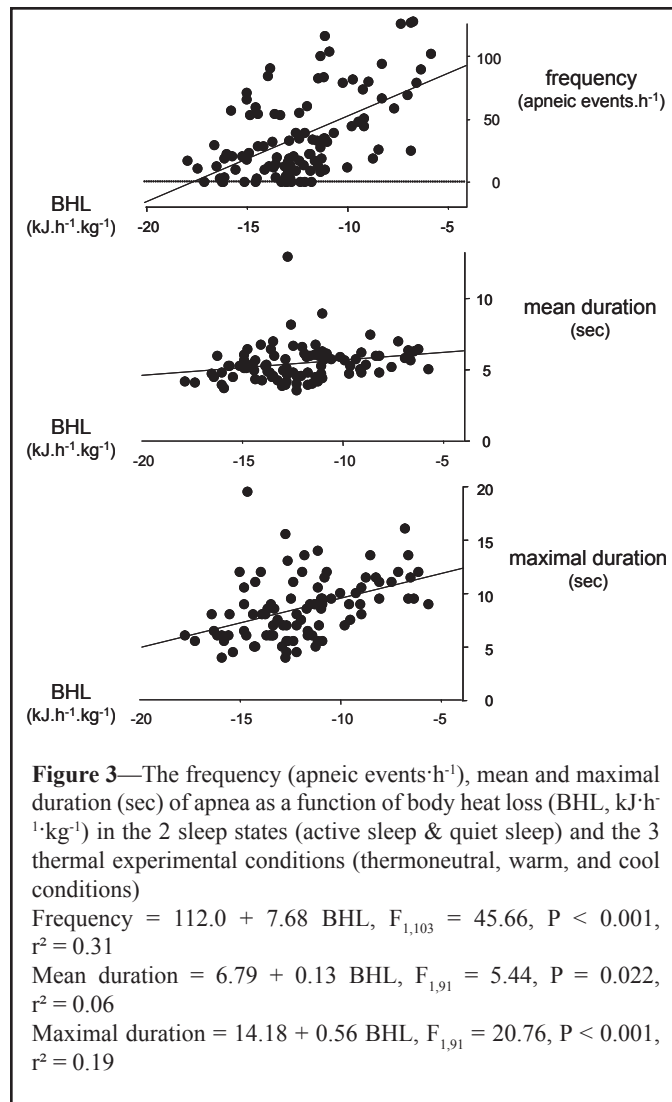


Figure 3—The frequency (apneic events·h⁻¹), mean and maximal duration (sec) of apnea as a function of body heat loss (BHL, kJ·h⁻¹·kg⁻¹) in the 2 sleep states (active sleep & quiet sleep) and the 3 thermal experimental conditions (thermoneutral, warm, and cool conditions)

Frequency = 112.0 + 7.68 BHL, $F_{1,103} = 45.66$, $P < 0.001$, $r^2 = 0.31$

Mean duration = 6.79 + 0.13 BHL, $F_{1,91} = 5.44$, $P = 0.022$, $r^2 = 0.06$

Maximal duration = 14.18 + 0.56 BHL, $F_{1,91} = 20.76$, $P < 0.001$, $r^2 = 0.19$

erature, cool exposure increases the relative duration of active sleep, at the expense of quiet sleep (reviewed in²⁶). In contrast, the few studies dealing with warm challenges have demonstrated that the latter lack a strong effect on sleep structure,²² in agreement with the present results. The increases in heart rate (+6 beats·min⁻¹) and mean skin temperature reflect the vasodilatory response to warm exposure.

Our results show that BHL is a more sensitive indicator of thermal stress than is rectal or mean skin temperature, since the typical increase in $\dot{V}O_2$ occurring on cool exposure is observed when BHL is greater, despite a higher rectal temperature and a nonsignificant change in mean skin temperature. This is easily explained by the fact that the internal temperature is not the same throughout body, and, therefore, determination of the loss of body heat is a more accurate estimation of thermal drive than are body temperatures themselves. This finding agrees with those based on pooled^{37,38} or individual data³⁹ and explains the fact that, in most studies performed on neonates, the expected negative correlation with $\dot{V}O_2$ is obtained with air temperature rather than body temperatures. Thus, the body temperatures should be viewed as the output of the thermoregulatory system instead of its input—the latter being more related to BHL.

Apneic Events and BHL

Of the 4000 recorded breathing pauses, only 75 lasted longer than 10 seconds and would be considered as clinically relevant (probably because the neonates were near term). The overall apnea frequency (36.2 ± 32.5 events·h⁻¹) is consistent with previous reports on preterm neonates.^{3,40}

The apnea frequency varies in both cool and warm conditions—evidencing an interaction between thermoregulatory and respiratory processes. As shown in Figure 2, the apnea frequency increased during warm exposure in active sleep only (in contrast with cool exposure, which decreased the frequency of apneic events in both active sleep and quiet sleep), evidencing a functional interaction between respiratory control and the sleep process. Disparities between active sleep and quiet sleep have already been reported: Franco et al⁸ found that the apnea frequency significantly increased with a warmer ambient temperature during active sleep in older neonates (between 37 to 41 weeks of gestation, median age: 11.5 weeks). Likewise, the mean duration of apnea was decreased by cool exposure in active sleep only.²² In contrast, Bader et al¹¹ reported that the rate of apneic events in active sleep increased with warmer ambient air temperature in full-term neonates but not in preterm neonates.

In warm exposure, an increased frequency of apneic events has been extensively reported.^{8,9,11,41} With the exception of the work by Bader et al¹¹, most of these studies did not look for (or did not demonstrate) significant warm thermal effects on apnea duration, as confirmed by our results when comparing thermoneutrality and warm exposure. The mechanisms of the impact of warm stimuli on apneic episodes have not been elucidated. Several hypothesis have been put forward: changes in autonomic control^{8,42} or bulbopontine mechanisms,⁴³ hypocapnia due to thermally induced hyperventilation,^{44,45} and the impact of more effective inhibitory inputs on breathing patterns.^{46,47}

BHL is the sum of conductive, convective, radiant, and evaporative heat losses. It is balanced by the metabolic heat production so that heat storage is nil. During active sleep, metabolic heat production (M) is equal to metabolic heat production during quiet sleep plus ΔM , extra heat production due to increased brain activity during this sleep stage. In the cool condition, metabolic heat production is increased through nonshivering thermogenesis and increased body activity. However, ΔM is assumed to be constant. Adding ΔM to BHL in active sleep does not bias the results. Indeed, the significant correlation between apneic event parameters and BHL (see below) was still significant when active sleep and quiet sleep were analyzed separately (always, $F_{1,44} > 5.21$, $P < 0.027$).

Interestingly, our present results indicate that apneic event rates or durations decrease when neonates are exposed to a cool thermal challenge (i.e., low BHL negative values).

In our study, the relationship between apneic parameters and the thermal drive is not related to body temperatures but, rather, to the BHL (for each thermal condition as well as in each sleep state), confirming the hypothesis of Perlstein et al.⁹ Although the regression coefficients for the different relationships were significant, they only explain between 6% and 31% of the observed variance. This emphasizes the physiologic variability commonly found in the growing organism, due to differences

in the ontogenesis adjustments resulting from neuronal and functional maturation. Prenatal and postnatal influences may also increase interindividual variability. Moreover, the absence of a warm thermal effect on apnea events during quiet sleep may also explain the low r^2 values observed. Lastly, partitioned calorimetry does not quantify the strength of the dependence of body heat exchanges on convective (h_c) and radiative (h_r) heat transfer coefficients, which are currently assumed to be constant—despite the fact that their values depend on body shape and the curvature of the body segments, which differ from one neonate to another. Moreover, despite standardization of the body posture, small changes in the position of the arms and legs can modify the effective skin surface area exchanging heat with the environment. This behavioral response cannot be taken into account in the calculation of the BHL. Despite this limitation, all of the relationships are highly significant and underline the importance of monitoring body heat exchanges when examining respiratory instability. The relationship between apneic events and BHL rather than with body temperatures may also explain why some authors have not found an increase in the number or duration of apneic episodes with increasing rectal temperature.^{48,49}

The greater the body cooling, the lower the frequency and the mean and maximal durations of apneic episodes. This suggests that breathing instability is less intense in a cool environment, when extra metabolic heat production is required to maintain body homeothermia.⁵⁰

The fall in the frequency and duration of respiratory pauses in the cool condition could favor the lung and blood oxygen stores that are required to fuel an increase of aerobic metabolism in response to a cool thermal challenge. Nonshivering thermogenesis is induced via sympathetic activation of the brown adipose tissue. This change in autonomic balance (in favor of the orthosympathetic system) could influence the frequency and length of apneic episodes. Indeed, several authors have evidenced a peak in muscle sympathetic nerve activity,⁵¹ abrupt tachycardia,⁵² or a steady increase in sympathetic activity (followed by a sudden reduction or cessation of this activity upon ventilation onset) during apnea.⁵³ This peak may help end the apneic event.

In conclusion, the results of the present study show that breathing instability during mild thermal challenges in near-term neonates is unrelated to levels of body temperature changes but is controlled by processes involved in BHL. These findings, if confirmed for pathologic apnea, suggest that manipulating the thermal environment, (at least in the thermal range considered in the present study) with a view to increasing BHL may be an additional or even alternative means of clinical apnea treatment and/or may significantly hasten the resolution of apneas of prematurity. It is unknown whether this thermal effect exists in older infants and, if so, whether it could be used in prevention of sudden infant death syndrome. Indirectly, prevention of apnea of prematurity (especially when associated with hypoxemia) soon after birth may, in turn, limit predisposition to further apneic episodes and, as a result, may reduce the risk of sudden infant death syndrome.⁵⁴ However, the occurrence of adverse side effects (such sleep alterations and a reduction in body mass gain) cannot be ruled out.^{21,26}

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