

# Body Temperatures, Sleep, and Hibernation

Kurt Kräuchi and Tom Deboer

## Chapter 28

### Abstract

The human sleep–wake cycle is usually tightly coupled to the circadian time course of core body temperature. The circadian regulation of heat loss in the evening, via distal skin regions, is intimately associated with sleepiness and the ease to fall asleep, whereas the homeostatic increase in sleep pressure does not influence the thermoregulatory system. The rise in heat loss and reduction in heat production during lying down and relaxing behavior before sleep is hypothesized to be part of the role of sleep as a mechanism for energy conservation and may be a remnant of our evolutionary past. After sleep initiation, non-rapid eye movement (NREM) sleep to rapid eye movement (REM) sleep cycle fluctuations seem to have minor thermoregulatory functions, especially in humans.

From experimental data obtained in humans and rodents, it can be concluded that warming can increase sleep propensity, sleep consolidation, and the duration of SWS (slow-wave sleep). In contrast, the effects of cooling on sleep are not yet sufficiently studied. More systematic investigations applying

different temperature levels, particularly in the range where thermoregulation is achieved solely by vasomotor responses (the thermoneutral zone), are needed to develop applicable thermal therapeutic strategies for sleep disturbances.

From anatomical and neurophysiological studies it has become clear that the preoptic-anterior-hypothalamus (POAH) is the main integrator of sleep and thermoregulatory information. It receives input from brain areas involved in circadian and sleep–wake regulation, and skin and brain areas recording body and environmental temperature. The POAH integrates this information and influences vigilance states and body temperature in response to that input.

The torpid state, particularly of those animals that display daily torpor, may be a valuable model to investigate the relationship between thermoregulation and sleep. During daily torpor, the animals seem to apply similar physiological processes as occur in humans during normal entrance into sleep, but in a more extreme way, providing an excellent opportunity to investigate these processes in detail.

### INTRODUCTION

The objective of this chapter is to cover the physiology of the relationship between the thermoregulatory system and the sleep regulatory system. Both are driven, independently, by two interacting physiological principles, homeostasis and circadian regulation. The chapter is divided in 3 main sections: 1) a brief introduction into the circadian regulation of core body temperature (CBT); 2) the interaction of sleep and thermoregulatory mechanisms; 3) hibernation, a special condition displayed by a limited amount of mammalian species.

Animals increase survival by residing in a safe sleeping site, and have used sleep to maximize energy savings by reducing body and brain energy consumption and to conduct a variety of recuperative processes.<sup>1,2</sup> Knowledge about thermophysiology and its relation to sleep leads to the hope that temperature related interventions can alleviate sleep disturbances and be helpful to cure certain aspects of sleep and alertness problems in the general population.

A vast amount of knowledge is found in the literature on the variability in rest–sleep states and on thermophysiology across the animal kingdom.<sup>1,2</sup> In order to limit the scope of this chapter, only findings from humans, rats, ground squirrels, and hamsters have been reviewed.

### CIRCADIAN REGULATION OF CORE BODY TEMPERATURE

Fifty years ago, Aschoff<sup>3</sup> showed that the human body consists of two thermophysiological compartments, the heat producing, homeothermic core, and the heat-loss regulating, poikilothermic shell. The size of the latter is largely dependent on environmental temperature. In a

warm environment the shell is small, in a cool environment large, and thus acts as a buffer to protect the core from dangerous cooling. All peripheral tissues such as fat, skin, and in particular skeletal muscles of the legs and arms can contribute substantially to the size of the shell, provided that peripheral blood flow is low. Therefore, rates of blood flow through muscles and skin are the main determinants of shell size variability and hence of peripheral insulation. The distal skin regions, in particular fingers and toes, are our main thermoeffectors to lose body heat as they possess the physical and physiological properties to best serve the function of heat loss. They have ideal surface shapes (round, small radius) for good heat transfer to the environment—the surface-to-volume coefficient increases from proximal to distal skin sites. Therefore, the distal skin temperatures provide a good measure of the shell size.

CBT comprises the temperature of the brain and the abdominal cavity, including inner organs (e.g., liver, heart, kidney).<sup>3</sup> In most placental mammals CBT is regulated around 37° C, whereas the brain is the main target for homeothermy allowing control of all behavioral and physiological processes over a broad environmental temperature range. A detailed description of the thermoregulatory system can be found elsewhere.<sup>4</sup>

CBT is regulated between thermoeffector thresholds, which are subject to circadian oscillations.<sup>5</sup> Circadian rhythms in mammals are generated by the self-sustaining central pacemaker localized in the suprachiasmatic nuclei (SCN) of the hypothalamus and are usually entrained to the 24-hour solar day mainly by the synchronizer light.<sup>6</sup> A rostral projection from the SCN to the preoptic-anterior-hypothalamus (POAH) conveys the circadian signal to the thermoregulatory system.<sup>6</sup> The regulation of CBT results from the concerted action of the homeostatic and circadian

processes. In humans, the daily decline of CBT in the evening results from a regulated decline in the thermoregulatory thresholds of heat production and heat loss; the inverse happens in the morning. When heat production surpasses heat loss, body heat content increases, and vice versa. Approximately 70% to 90% of body heat content is located in the body core, depending on environmental temperature; therefore, changes in CBT reflect to a great extent changes in body heat content. Heat production and heat loss are modified by activities such as muscular exertion and fluid and food intake that are not randomly distributed over the circadian cycle. These behaviors induce so-called masking effects, and differentially modify the endogenous rhythm of CBT.<sup>7</sup>

In order to disentangle circadian from masking effects of an overt diurnal pattern, the constant routine (CR) protocol has been developed in humans.<sup>8</sup> With this protocol it was shown that the time course of heat production precedes heat loss, and CBT varies as an intermediate resultant.<sup>8</sup> Heat production and heat loss are not only separated in time but also in space in the body.<sup>3</sup> Under resting conditions, about 70% of heat production depends on the metabolic activity of inner organs, whereas body heat loss is initiated via heat redistribution from the core to the shell through blood flow to the distal skin regions.<sup>3</sup> Thermoregulatory distal skin blood flow is regulated by the autonomic nervous system via constriction or dilatation of arteriovenous anastomoses. These are shunts between arterioles and venules, exclusively found in distal skin regions (e.g., toes, fingers).<sup>3</sup> When they are open, warm blood flows rapidly and directly from arterioles to the dermal venous plexus enabling an efficient heat exchange from the core to the distal skin. The exact neural process by which this regulation is achieved is still a matter of debate<sup>9</sup>; however, sympathetic nerve activity seems to be crucial for peripheral vasoconstriction. The endogenous time course of distal skin temperatures (hands and feet), measured during a CR, exhibits an inverse circadian rhythm in comparison with CBT, whereas the former is phase advanced by about 100 minutes<sup>8</sup> (i.e., in the evening distal skin temperatures rise before CBT declines). The amplitude of distal skin temperatures rhythm is about three times larger than those of CBT.<sup>8,10</sup> In contrast, temperatures of proximal skin regions (e.g., thigh, infraclavicular region, stomach, forehead) follow a parallel change to CBT and the amplitudes are of similar magnitude.<sup>8,10</sup> This inverse relation between distal and proximal temperature rhythms reflects the differences in thermophysiological regulatory mechanisms as described above.<sup>3</sup> The distal minus proximal skin temperature gradient (DPG) provides therefore a selective measure of distal skin blood flow, and hence body heat loss via the extremities.<sup>3</sup>

Nocturnal secretion of the pineal hormone melatonin, which is under control of the SCN, plays a crucial role in the endogenous downregulation of CBT in the evening.<sup>11</sup> Administration of melatonin in the afternoon, when endogenous melatonin levels are low, provokes exactly the same thermophysiological effects as observed naturally in the evening.<sup>11</sup> Whether melatonin induces distal vasodilatation in humans by acting directly on blood vessels receptors or indirectly via modulation of sympathetic nerve activity, or both remains to be determined.<sup>11</sup> In addition,

both subjective ratings of sleepiness and level of activity in the electroencephalographic (EEG) theta and alpha range as an objective outcome of sleepiness–wake state, are increased.<sup>11</sup> Moreover, it is noteworthy that the rise in melatonin secretion in the evening belongs to a well-orchestrated circadian physiological regulation controlled by the SCN, which in turn downregulates CBT, increases sleepiness, and promotes sleep.

## RELATIONSHIP BETWEEN THE SLEEP REGULATORY AND THE THERMOREGULATORY SYSTEM

The most evident explanation whether and why the sleep regulatory and thermoregulatory systems are interrelated is a teleological one: sleep is for energy conservation.<sup>2,12,13</sup> All species sleep or rest when their energy expenditure is low. Rest or quiet wakefulness, is a prerequisite for sleep in all species.<sup>1,12,13</sup> These observations represent the starting point of all energetic explanations why we sleep. Human sleep evolved from ancestral sleep and it is quite possible that earlier forms of sleep were linked to energy conservation in ancestors with a smaller body size.

There are two mechanisms that enable sleep to conserve energy. One is that sleep reduces energy expenditure indirectly by reducing activity. This mechanism would also be active when animals only exhibit quiet wakefulness. Alternatively sleep induces an additional decline in energy expenditure below that accomplished by quiet wakefulness by a change in physiology. Human sleep is only accompanied by a modest decline in energy expenditure below the level of quiet waking.<sup>13–15</sup> However, energy conservation may be particularly important in small animals and infants.<sup>2,13,16</sup> Their high surface-to-body-mass ratio is ideal to dissipate heat and renders energy conservation achieved by sleep highly adaptive.<sup>13</sup> When body size increases and sensory-motor systems mature in the course of infant development, a parallel decrease in sleep time occurs.<sup>2,16</sup>

In the following subsections, two lines of evidence will be presented to clarify the relationship between sleep and thermoregulatory systems: 1) at baseline thermal *comfort* condition; and 2) following various conditions such as circadian, temperature, sleep pressure changes. Furthermore, recent research has provided new insights into the relationship between thermoregulation and sleep on the basis of neuroanatomical studies showing significant interaction of the two systems.

### Co-variation of Sleep and Thermophysiological Variables

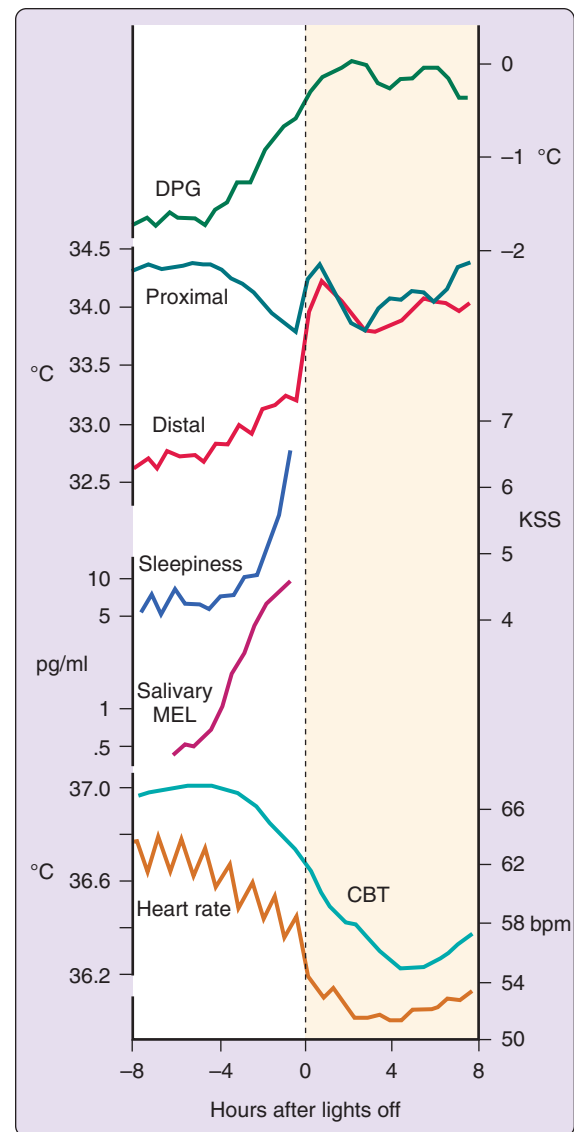
#### BASELINE CONDITIONS

In order to compare the sleep and thermoregulatory systems it is crucial to separate circadian from masking components of an overt diurnal pattern. This is much easier to accomplish in humans than in animals. In spite of this advantage, the most neglected factor in human research is the so-called lying down effect. A change from standing to supine body position induces redistribution of heat from the core to the periphery, thereby increasing skin temperatures, decreasing CBT, and in parallel increasing sleepiness.<sup>17</sup> This effect lasts about 1 to 2 hours,<sup>17</sup> and significantly confounds the endogenous time course of CBT in a

classical sleep recording protocol where lying down occurs about 0.5 hours before lights off. The temporal relationship between thermophysiological variables, heart rate, subjective ratings of sleepiness and salivary melatonin secretion under CR conditions before habitual bedtime and for the following sleep episode is summarized in Figure 28-1. The only thing that changed during this protocol was that the low intensity lights were switched off with the implicit permission to fall asleep. Before lights off the previously described endogenous pattern of CBT down regulation is visible. In the evening, heart rate (an indirect measure of intrasubject variation of heat production) declined first, followed by heat loss, and finally by a decrease in CBT. Subjective ratings of sleepiness increased in parallel with distal proximal gradient (DPG) and salivary melatonin levels. The proximal skin temperature exhibited a similar pattern as CBT. Immediately after lights off, and before sleep stage 2, distal and proximal skin temperature increased and heart rate declined.<sup>18</sup> In addition, an increase in sweating rate is often observed, depending on CBT.<sup>19</sup>

The typical increase in distal skin temperature, as shown in Figure 28-1, is caused by heat redistribution from the core to the shell. Similar findings at sleep onset have been described in the lower leg.<sup>20</sup> However, CBT exhibited only a slight but significant increase in the rate of change after lights off,<sup>3,21</sup> leading to approximately 0.3° C lower CBT values during sleep compared to quiet wakefulness.<sup>22</sup> In contrast to the fast changes in skin temperature, the decline in CBT is slow, which can be explained by the reduced cardiac output during sleep initiation impeding a faster heat loss during the sleep episode, under thermoneutral conditions.<sup>18</sup> The magnitude of the decrease in CBT is negatively correlated with environmental temperature.<sup>23</sup> A DPG of 0° C indicates that during sleep, the thermoregulatory shell has disappeared, therefore resembling a state similar to that of the human body in awake state in a warm environment (e.g., 35° C).<sup>3</sup> Heat redistribution from the core to the shell is completed within approximately 1 hour after lights off. Such a completely relaxed one-compartment body is prone to a fast cooling when sleep occurs in a cool environment. In normal sleep environment, CBT is protected during sleep because humans and animals try to occupy a sleep berth in a comfortable thermal environment.<sup>13</sup> When sleep is initiated outside the natural temporal niche by taking an afternoon nap, similar thermophysiological changes occur right after lights off and before the initiation of sleep stage 2.<sup>24</sup> There are subjects, mostly women, exhibiting a proneness to cold hands and feet and, therefore, to a large shell.<sup>25,26</sup> These subjects show a significant co-morbidity for prolonged sleep stage 2 onset latency (SOL2).<sup>25,26</sup> In fact, it has been shown that subjects with sleep onset insomnia respond to a mild heating with reduced thermoregulatory heat loss from their fingers.<sup>27</sup>

After a sleep episode, transition to waking is accompanied by an inverse thermophysiological pattern.<sup>24</sup> This period is named sleep inertia; after awakening it takes a certain time interval to recover all physiological and cognitive functions.<sup>24</sup> During that time, a similar but inverse time course in distal vasoconstriction is observed.<sup>24</sup> It is noteworthy and of clinical relevance that similar thermophysiological effects as seen during sleep initiation can be



**Figure 28-1** Time course of heart rate core body temperature (CBT), and its rate of change, salivary melatonin, sleepiness, distal and proximal skin temperatures, and the distal-proximal skin temperature gradient (DPG) in a baseline 7.5-hour constant routine followed by a 7.5-hour sleep period, *yellow area*. (Adapted from Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. Functional link between distal vasodilation and sleep-onset latency? *Am J Physiol Regul Integr Comp Physiol* 2000;278(3):R741-R748.) Continuously measured data are plotted in 30-minute bins. Mean values of  $N = 18$  male subjects ( $\pm$  SEM). Subjective ratings of sleepiness: KSS, Karolinska sleepiness scale; MEL, melatonin; bpm, beats/min. Note: Distal and proximal skin temperatures exhibit inverse time course before lights off, but were nearly indistinguishable about 1 hour thereafter. Heart rate reflects the study protocol rhythm of one hourly food and water intake before lights off and declined sharply thereafter. Mean sleep onset latency: 12 minutes  $\pm$  4 minutes.

observed after administration of benzodiazepines<sup>28</sup> and with certain relaxation techniques like yoga, autosuggestion of warmth, autogenic training, and meditation without falling asleep.<sup>3,28-30</sup> These techniques induce a withdrawal in muscular and cutaneous sympathetic nerve activity, which leads to increased distal skin temperature and to a

reduction in heart rate, energy expenditure, and CBT.<sup>28,29</sup> Therefore, distal vasodilatation followed by a drop in CBT appears to be a thermophysiological event, which is primarily related to relaxation occurring before sleep onset.<sup>31</sup>

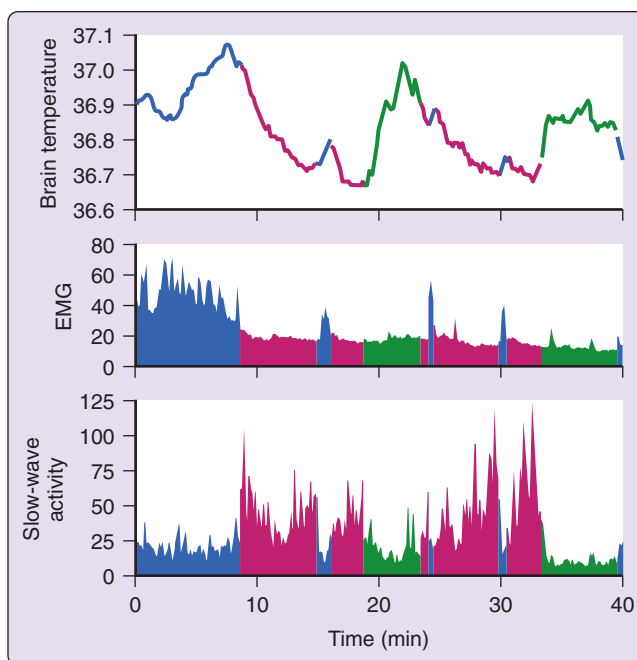
Studies carried out with humans to describe changes in thermophysiological variables show that changes in CBT, proximal and distal skin temperature related to the NREM-REM sleep cycle are very small.<sup>32,33</sup> Heart rate is clearly increased shortly before and during REM sleep, relative to NREM sleep, which is, however, reflected only in a minor increase in energy expenditure during REM sleep.<sup>15</sup> Extensive studies on thermophysiological alterations regarding the NREM-REM sleep cycle, concluded that changes in brain heat production are practically not relevant for changes in brain temperature.<sup>34</sup> To our knowledge, only one human study recorded brain temperature together with sleep-EEG data, but no significant systematic changes regarding the NREM-REM sleep cycle were found.<sup>35</sup>

One of the advantages of animal research is the parallel recording of body and brain temperature. In many small mammals (rabbit, rat, Djungarian hamster) NREM sleep is associated with a decrease in brain temperature, whereas REM sleep and waking are associated with an increase in brain temperature (Fig. 28-2).<sup>36,37</sup>

In an elegant study performed with rats it was shown that heat is redistributed across the body when vigilance states change.<sup>38</sup> At the initiation of NREM sleep, the brain and intraperitoneal temperature decreased whereas the tail skin temperature increased. The opposite occurred at the transition from NREM sleep to awake. At transitions from NREM sleep to REM sleep, brain temperature rose slightly, whereas intraperitoneal and tail temperatures did not change. These data are in accordance with those obtained in humans. Heat is redistributed from the core to the shell at the onset of sleep. Humans thermoregulate by vasodilatation and vasoconstriction of blood vessels within the skin of extremities; in rats similar changes are observed in the tail. The main difference lies in the timing of the redistribution of heat relative to the onset of sleep and waking. In humans changes are visible several hours before sleep onset; in the rat the same changes occur at the immediate onset of sleep. This difference is probably related to the smaller body size and to the ultradian sleep-wake pattern in the rat that renders a time-lag of several hours to be nonfunctional.

Applying a CR in rodents is not possible. However, on the basis of the relationship between brain temperature and vigilance states, it was possible to subtract the influence of vigilance state changes on brain temperature, rendering a mathematical CR.<sup>39</sup> This study concluded that, in the rat, approximately 90% of the variance in brain temperature is caused by changes in vigilance. A recent study confirmed that vigilance state-related changes in brain temperature are independent of the functioning of the circadian clock because they remained intact after removing the SCN.<sup>40</sup>

Taken together, there are robust thermoregulatory effects induced by lying down and the relaxing sleep behavior, however, the NREM-REM sleep cycle seems to have minor thermoregulatory function in humans. The thermoregulatory mechanisms, which are active during the wake-sleep transition, redistribute heat from the core to the shell



**Figure 28-2** A 40-minute record of brain temperature measured at the parietal cortex, integrated EMG activity from the neck muscles, and EEG slow-wave activity (SWA, mean EEG power density between 0.75 Hz and 4.0 Hz), of a Djungarian hamster (*Phodopus sungorus*). Blue = waking, Red = NREM sleep, Green = REM sleep. Values are plotted for 8-second epochs. Note the decrease of brain temperature at the entrance into NREM sleep and the increase during REM sleep and waking.

and induce a decline in heart rate, energy expenditure,<sup>14,15</sup> and CBT. Relaxing behavior before sleep belongs inseparably to sleep; therefore, these data are not in contradiction with the energy conservation hypothesis of sleep. The accompanying thermoregulatory effects in humans may be a remnant of their evolutionary past.

#### CHANGED CIRCADIAN CONDITIONS

It has been observed that subjects living under normal conditions choose their bedtime (lights off) at the maximal rate of decrease in their CBT rhythm.<sup>41</sup> However, when subjects are living on self-selected sleep-wake schedules in a time-free environment, bedtime is phase delayed close to the CBT minimum, which is an indication that the sleep-wake cycle and the circadian rhythm of CBT are separate but usually entrained (synchronized) oscillatory systems.<sup>42</sup> Unfortunately, neither direct nor indirect measurements of heat loss and heat production were carried out in parallel in these studies. Therefore it is possible that CBT is not the crucial variable for sleep induction, but rather one of its determinants, that is, heat loss. Because heat loss seems to be closely linked to sleep initiation, it may be speculated that the circadian rhythm of heat loss is phase delayed under free-run conditions. The duration of sleep episodes was maximal when initiated at the time when CBT reaches its maximum and, at the opposite, minimal sleep lengths occurred when sleep was initiated during the rising phase of the CBT rhythm.<sup>16</sup>

There is also a reproducible and robust circadian rhythm in sleep onset latency to sleep stage 2 (SOL2), which is

closely related to the circadian CBT rhythm and thermoregulatory effects as described previously.<sup>43</sup> In forced desynchrony studies (i.e., living on a scheduled 28-hour day including a 9.33- to 18.66-hour sleep-wake cycle) it was shown that SOL2 is longest at the circadian phase where CBT reaches its maximum, that is, 1.5 hours before CBT starts to decline and melatonin secretion rises.<sup>44</sup> At this circadian phase, named the “wake-maintenance zone,”<sup>45</sup> inner heat conduction is lowest as indicated by largest difference between CBT and distal skin temperature, as well by largest negative DPG values. Thereafter, SOL2 declines rapidly and is minimal around the time when CBT reaches its circadian trough, when inner heat conduction is largest (distal skin temperature is highest and the difference between CBT and distal skin temperature is lowest). However, it remains to be determined whether thermal interventions, like lower leg warming, at the wake-maintenance zone are successful to reduce SOL2, as melatonin administration was shown to do.<sup>46</sup>

Under most experimental conditions, REM sleep propensity exhibits a strong circadian pattern with a peak approximately 1 to 2 hours after CBT has reached its circadian minimum.<sup>44</sup> The circadian rhythm of REM sleep propensity is closely phase locked with the circadian rhythm of CBT with a phase lag of 1 to 2 hours.

Taken together, self-selected sleep timing, SOL2, REM sleep latency, REM sleep propensity, and sleep duration are closely associated with CBT. In spite of the fact that these variables are not fully in phase with CBT, which precludes a direct link to CBT, it is quite possible that one of the determinants of CBT (e.g., heat production, heat loss) is directly interrelated. It still remains to be established whether these rhythms are independently governed by the SCN or causally linked directly to measured thermophysiological outcomes. These correlative findings lead to the question of how sleep is affected by thermoregulatory challenges.

### *Intervention Studies in Humans*

Effects of thermal interventions (heating or cooling) on sleep are not easy to investigate. Thermal intervention, either applied passively or actively by physical exercise, induces significant changes in skin temperatures and CBT.<sup>14,16,47,48</sup> Not only is the intensity of a thermal intervention crucial, but also the skin region selected and the time of application. During sleep only passive thermal loads can be applied. It has been shown that sleep reduces the thresholds and gains of the autonomic temperature defense mechanisms and expands the inter-threshold zone (the temperature range for activation of metabolic heat production or evaporative heat loss).<sup>16,48,49</sup> These threshold changes are modest in slow-wave sleep (SWS), but much stronger in REM sleep.<sup>16,48</sup> As a consequence, CBT and skin temperatures are more sensitive to changes in environmental temperature. Maximal total sleep time (TST) is found in the thermoneutral zone (the range of ambient temperature at which temperature regulation is achieved solely by vasomotor responses), whereas REM sleep is more vulnerable to thermal interventions than is SWS.<sup>16,48</sup> Too powerful of thermal interventions induce arousals and awakenings, which in turn can change thermoregulatory effects, for example,

elevating CBT.<sup>48</sup> When a thermal load is given repeatedly, the thermoregulatory system can adapt and the effects on sleep are changed; for example, the arousing effects are reduced. Aborigines in the Central Australian desert and nomadic Lapps in Arctic Finland were experiencing comparable degrees of cold exposure during the night and both showed lower thermoregulatory thresholds for shivering before modern technology arrived.<sup>50,51</sup> As a consequence, CBT was more reduced during sleep and undisturbed sleep occurred at a lower environmental temperature. Many modalities of thermal interventions on sleep are understudied. In addition, the impact of thermal interventions on the sleep of normal and sleep-disturbed subjects may differ.

### CHANGING TEMPERATURES

It has been shown that ambient temperature, especially in combination with high humidity, is of importance for both quantity and quality of sleep.<sup>48</sup> When sleep occurs in warm environmental temperature (between 31° C and 38° C) duration of wakefulness increases and, at the opposite the duration of REM sleep and NREM sleep decreases.<sup>14,16,47,48</sup> Also cold exposure (21° C) induced more awakenings, less time in sleep stage 2 and less TST; however, without affecting duration of other sleep stages, marked thermoregulatory effects were induced under such manipulations.<sup>14</sup> The decrease in CBT observed during the night episode was larger at 21° C compared to a thermoneutral 29° C condition. During REM sleep, forehead temperature and oxygen consumption increased and feet temperature decreased in comparison to SWS with cold exposure. Therefore, cold-exposed humans may not exhibit a complete inhibition of thermoregulation during REM sleep as it has been observed in small mammals.

When during sleep the ambient temperature is gradually decreased, an earlier CBT nadir and an advanced peak for REM sleep propensity was obtained.<sup>52</sup> It was also shown that duration of sleep stage 4 is increased when the normal nocturnal decrease of CBT is augmented by a constant and mild reduction in ambient temperature, in spite of decreased sleep efficiency.<sup>52</sup> Similarly, after a reduction in ambient temperature by 2° C during sleep, it was observed that the increase in SWS occurred with the rise in slow-wave activity (SWA; EEG power density between ~1 to 4 Hz) without any change in sleep efficiency and reduced amount of REM sleep.<sup>53</sup> The thermal manipulation reduced not only leg skin temperature but also CBT and heart rate. Taken together, the augmentation of heat loss leading to reduced CBT during sleep seems to be the crucial variable for increased SWS.

In humans, body heat content and hence CBT can also be effectively manipulated by body immersion in warm or cold baths. For instance, due to rapid conductive heat loss in a cold bath, CBT falls faster compared with that observed in air at the same temperature. Rewarming of the cool shell after cool bathing leads to a characteristic after-drop in CBT.<sup>54</sup> Several studies showed effects of positive heat load on sleep;<sup>14,47,48</sup> however, no study examined effects on sleep after a cold bath. In general, passive body heating (40° to 43° C for 30 to 90 minutes; CBT increase: 1.4° to 2.6° C) has a positive effect on many aspects of sleep in healthy young adults and in older and

sleep-disturbed subjects. It was found that warm bathing in the evening shortened sleep onset latency, enhanced SWS duration, and sometimes reduced REM sleep duration. The increase in SWS, however, is not dependent on a reduction in REM sleep. Bathing performed in the morning or early afternoon had no effect on sleep architecture.<sup>14,47</sup> In principle, actual levels of CBT at sleep onset or the decline in CBT afterward could be related to the amount of SWS after warm bathing.<sup>14,47</sup> Additionally, a phase delay of the CBT nadir during the night sleep episode has been described after evening hot bathing, which correlates with increased SWS.<sup>55</sup> All these CBT characteristics could be intercorrelated (i.e., directly after a positive heat load the velocity of CBT decline is larger, the CBT level is elevated before sleep onset and the overt CBT nadir during sleep may be delayed). However, the phase shifting effects of passive heat loads in humans have not been studied systematically. Variables other than CBT, for instance skin temperature, may play a role. The available findings are inconsistent due to the diversity in study designs and methodology and the low statistical power of many studies. In one study, hot full-body bathing and hot foot bathing were applied 35 minutes before lights off.<sup>56</sup> Only during full-body bathing did CBT increase (by about 1° C); however, both conditions increased mean skin temperatures and reduced sleep onset latency and movement during sleep. These findings indicate that elevated skin temperature is crucial for a rapid onset of sleep and not changes in CBT. Older sleep-disturbed subjects respond to hot foot bathing with slightly reduced sleep onset latency (SOL) to sleep stage 1 and significantly decreased wakefulness in the second NREM sleep period.<sup>57</sup> In these older subjects, not only DPG but also CBT was elevated after hot foot bathing during the first hour of sleep.

Of clinical relevance is the data describing that the use of electric heat blankets throughout the night reduced REMS duration and TST,<sup>58</sup> suggesting that the heat load exerted through the blanket is a too-strong thermal intervention that disturbs sleep rather than supports sleep. In a series of experiments, the effects of tiny changes in skin temperatures of only 0.4° to 2° C within the thermal comfort zone, without significantly altering CBT, were investigated on several sleep parameters.<sup>59</sup> It was demonstrated that intermittent elevation in skin temperature during the sleep episode suppresses nocturnal awakenings and triggers shifts to deeper sleep in young and older healthy subjects and in insomniac patients.<sup>59</sup> Whole-night studies are needed to confirm that the sleep-depth enhancing effect of mild skin warming can indeed be sustained. Nevertheless, these findings support the importance of skin temperatures, primarily proximal skin temperatures (including the trunk) but also more distal skin regions, such as legs and arms, for these effects. Other studies revealed that subtle skin temperature warming was associated with a faster onset of sleep in young and older subjects and in older insomniac and narcoleptic patients.<sup>59-61</sup> At present stage, it cannot be concluded which thermophysiological correlate represents the causal factor to increase SWS and reduce SOL. Nevertheless heat load before sleep seems to increase the propensity of SWS.

Intense exercise is a manipulation that can also raise CBT by 2° C or more. Subsequently, CBT declines as a result of the thermoregulatory heat loss drive via increased vasodilatation and sweating. A number of reproducible exercise-induced changes on sleep have been identified after exercise in the evening: shortened SOL, increased TST and SWS, longer REM sleep onset latency and less REM sleep.<sup>62,63</sup> Exercise exhibits negative effects on sleep when performed close to the start of sleep—the optimal temporal positioning of physical activity is thought to be between 4 and 8 hours before bedtime.<sup>63</sup> Chronic exercise studies have not provided much stringent evidence of a sleep promoting effect. Conversely, with reduced exercise load in trained athletes, SWS and REM sleep onset latency were reduced, and REM sleep duration and SOL were increased.<sup>64</sup> Taken together, after intense exercise, sleep appears to commence faster and is deeper.

In conclusion, warm distal skin temperatures either induced by endogenous circadian heat loss regulation in the evening, homeostatic downregulation of CBT after passive and active heat load, or selective skin warming predisposes a rapid onset of sleep. More sophisticated studies with respect to skin regions are necessary to show which areas (e.g., shoulder, stomach, legs, hands, or feet) should be warmed to exhibit the strongest effects on sleep initiation and sleep architecture. The increase in skin temperatures could be the causal factor for the acceleration of sleep onset and the increase of SWS. Further studies must investigate the optimal time-interval between thermal intervention and bedtime and which physiological mechanisms are involved in the observed effects. It is possible that thermal afferents provide a signal for the sleep-inducing brain regions in the hypothalamus.<sup>28,65</sup>

#### CHANGING SLEEP PRESSURE

The studies of sleep deprivation effects on the thermoregulatory system cannot be understood without considering the circadian time at which the deprivation is occurring. All thermophysiological variables undergo significant circadian changes. Additionally, the effects of an experimental overnight sleep deprivation on the thermoregulatory system have to be controlled for changes in body position, locomotor activity, food intake, and light intensity. Using the CR-protocol, it was shown that a 40-hour total sleep deprivation does not change CBT, distal and proximal skin temperatures, heart rate, and energy expenditure in spite of the huge increase in sleepiness.<sup>8,10</sup> A comparison with a sleep-pressure-reducing protocol, including regularly scheduled naps, provided evidence that changes in sleep pressure do not influence the thermoregulatory system.<sup>10</sup> Additionally, the nocturnal 8-hour sleep episodes before and after the two protocols revealed that CBT and distal and proximal skin temperatures also did not differ even though a large difference in SWA was observed.<sup>10</sup> Taken together, the circadian modulation of sleepiness is primarily related to the circadian regulation of distal vasodilatation and hence to heat loss and circadian CBT reduction, whereas the homeostatic regulated increase of sleep pressure does not influence the thermoregulatory system,<sup>18</sup> as earlier suggested.<sup>66</sup> To be more conclusive, longer sleep deprivations may need to be performed to test whether the

thermoregulatory system remains independent of sleep pressure.

### Intervention Studies in Rodents

#### CHANGING TEMPERATURE

The main interventions applied in rodents are manipulation of ambient temperature and manipulation of brain temperature. In the rat a general decrease in the daily percentage of REM sleep was seen when ambient temperature decreased,<sup>38,67</sup> indicating that REM sleep is very sensitive to changes in temperature and is incompatible with low ambient temperature. Djungarian hamsters enter REM sleep easier when brain temperature is relatively low,<sup>68</sup> but probably also in this species REM sleep will disappear first when ambient temperature is lowered. In this context, low ambient temperatures are applied as a tool to investigate REM sleep regulatory mechanisms.<sup>69,70</sup>

In general the impression exists that increasing ambient temperature increases sleep pressure. When ambient temperature was increased to 33° to 35° C for 3 hours, which resulted in a brain temperature of approximately 40° C, subsequent NREM sleep displayed more slow waves compared to sleep-matched controls.<sup>71</sup> The amount of REM sleep did not change compared to controls, and brain temperature was significantly decreased in the first 5 hours of recovery. Under these conditions animals slept less during the heating compared to baseline, indicating that ambient temperatures that are too high override sleep demand.

In two separate experiments where ambient temperature was increased to 30° to 32° C for 24 hours, cortical brain temperature was significantly increased by 0.3° to 1.0° C, but hypothalamic temperature did not change.<sup>72,73</sup> This treatment resulted in one case in increased NREM sleep, and in both experiments it resulted in an increase in SWA in NREM sleep in the dark period. These data indicate that changes in sleep can be induced by increasing ambient temperature without changing hypothalamic temperature.

Another approach is heating the POAH and increasing hypothalamic brain temperature locally, without changing ambient temperature. This approach resulted in increased SWA and NREM sleep during 1 hour of warming (1.0° C above baseline) in cats.<sup>74</sup> One hour of cooling (2.0° C below baseline) did not elicit a response. The data suggest that an acute increase in ambient or brain temperature (0.3° to 1.0° C) can increase NREM sleep and possibly can increase the occurrence of SWA in the NREM sleep EEG.

#### CHANGING SLEEP PRESSURE

During sleep deprivation, brain temperature is higher compared to baseline, and subsequent recovery is characterized by a decrease in brain temperature below baseline and an increase in NREM sleep and SWA in NREM sleep.<sup>37,73,75,76</sup> This result was interpreted as a heat load incurred during the sleep deprivation which is subsequently recovered by increasing NREM sleep and SWA.<sup>66</sup> One of the clear results obtained from these experiments is a negative correlation between the amount of NREM sleep and the level of brain temperature.<sup>68,75</sup> There is, however, no significant correlation between SWA in NREM sleep and brain temperature,<sup>68,75</sup> ruling out the

possibility that the depth of sleep determines brain temperature directly. Moreover, in Djungarian hamsters, which are well adapted to a short winter photoperiod when brain temperature is 1° C below summer photoperiod brain temperature, recovery sleep after sleep deprivation is accompanied by an increase in brain temperature.<sup>68</sup> This is in contrast with the long photoperiod where sleep deprivation is followed by a decrease in brain temperature.<sup>37,68</sup> A correlation between SWA and brain temperature, combining these data, supported the notion that brain temperature after sleep deprivation is set to the same temperature in both conditions,<sup>68</sup> suggesting that there may be an optimal temperature for high-amplitude slow waves in NREM sleep during recovery.

Two experiments that used rats and raised ambient temperature to 32° C during a sleep deprivation of 2.5 hours<sup>73</sup> or 3 hours<sup>76</sup> did not result in similar outcomes. Short lasting increases in SWA and NREM sleep were observed after 2.5 hours of sleep deprivation,<sup>73</sup> but not after 3 hours of sleep deprivation.<sup>76</sup> In contrast, a short-lasting increase in REM sleep was observed after the 3-hour sleep deprivation,<sup>76</sup> but not after the 2.5-hour sleep deprivation.<sup>73</sup> It can be questioned whether consistent results can be obtained in the rat with these short sleep deprivation durations. Probably a more systematic approach, scanning different ambient temperatures with longer sleep deprivations, is needed to resolve these differences.

#### BRAIN TEMPERATURE, EEG, AND THERMO-SENSITIVE NEURONS

The EEG is influenced by changes in brain temperature as well. From analysis of the EEG of the Djungarian hamster during spontaneous entrance into the hypothermic state torpor (see section on hibernation), and from experiments where either rats, cats, or humans were cooled, it was found that the amplitude and frequency of the EEG changes when brain temperature decreases. The amplitude becomes smaller, and prominent frequencies in the EEG slow down with decreasing temperature.<sup>77</sup> This relation between EEG frequency and brain temperature was shown to follow a  $Q_{10}$  of approximately 2.5,<sup>78</sup> which means that the frequency became 2.5 times slower when brain temperature decreased by 10° C. Under influence of euthermic changes this effect is relatively small, but it can be significant even for frequencies below 5 Hz.<sup>77</sup> Frequencies like the theta rhythm (6 to 9 Hz) in rodents<sup>77,79</sup> and frequencies above 10 Hz<sup>77</sup> are significantly influenced by these daily changes in brain temperature.

Measuring the electrical activity of neurons in the POAH revealed the activity of two distinct types of neurons that either increase or decrease firing rate when brain temperature increases. The latter are called “cold sensitive” neurons, whereas the first group are called “warm sensitive” neurons. A biochemical process (i.e., neuronal firing) that slows down when temperature is increased is quite unique; therefore, cold sensitive neurons, when observed, can be considered genuine. In contrast, a biochemical process that speeds up when temperature is increased is quite normal and has been theoretically explained at the end of the 19th century.<sup>77</sup> Many processes, ranging from the firing rate of SCN neurons<sup>80</sup> and the frequency of prominent EEG waves<sup>77</sup> to muscle

contraction,<sup>81</sup> double or triple when temperature is increased by 10° C ( $2 < Q_{10} < 3$ ).

To identify warm sensitive neurons, two definitions are applied in the literature. The first determines that an increase in firing rate needs to be more than double when temperature is increased by 10° C ( $Q_{10} > 2$ ).<sup>82</sup> The second says that the increase in firing rate needs to be more than 0.8 impulses/sec/1° C warming.<sup>83</sup> Both are insufficient. The definition of a  $Q_{10}$  above 2 ignores the fact that most biochemical processes have a  $Q_{10}$  somewhere between 2 and 3. Therefore,  $Q_{10}$  of at least 3 needs to be reached before one can be relatively sure that the change in firing rate can be distinguished from the passive biochemical response of the temperature insensitive neurons. With the second definition, fast firing neurons have a relatively large chance to be included even when they follow the passive biochemical  $Q_{10}$  rule of doubling firing rate when temperature is increased by 10° C. Nevertheless, there are genuine warm sensitive neurons in the POAH<sup>84</sup> and other brain areas, like the diagonal band.<sup>85</sup>

The firing rate of warm and cold sensitive neurons in the POAH is known to be vigilance-state-dependent. Most warm sensitive neurons increase their activity at the onset of NREM sleep. On the other hand, most cold sensitive neurons are more active during waking.<sup>84,85</sup> Those results emphasize the importance of polysomnographic recordings to be able to disentangle the vigilance-state-related changes in firing rate from temperature related changes.<sup>86</sup> Noradrenergic afferents from sleep-wake regulatory centers like the locus coeruleus and the lateral tegmental system are also involved in the change in firing rate observed in the POAH.<sup>87</sup> The changes in firing rate of the ensemble of neurons are thought to shape the sleep-wake response to thermoregulatory demands encountered by the animal.

## HIBERNATION

The hypothermic state observed during the hibernation season may be a valuable model to investigate the relationship between thermoregulation and sleep and may generate relevant data to the understanding of human physiology. Most hibernating mammals are small and weigh between 10 grams and 1000 grams.<sup>88</sup> During the hibernation season these animals spend a considerable amount of time in a torpid state with body temperature below euthermic temperatures (i.e., below 30° to 32° C). This sustained hypothermic state is entered voluntarily and can be terminated by the animal. Body temperature can drop by more than 35° C,<sup>89</sup> and the metabolic rate is only a fraction of that during normothermia.<sup>90</sup>

In hibernators the torpid state can last for several days or weeks. A group of smaller mammals with body weights between 5 grams and 50 grams displays daily torpor in which body temperature is dropped for a couple of hours during the rest phase, but returns to euthermia during the active phase.<sup>88</sup> Both hibernation and daily torpor result in substantial energy savings<sup>91,92</sup> and are therefore considered to be adaptive mechanisms that permit the conservation of energy during unfavorable environmental conditions.

Whether circadian rhythms continue during hibernation is unclear. In hibernating ground squirrels, rest-activity

rhythms only slowly reappeared a couple of days after termination of torpor bouts, and this correlated with the number of vasopressin containing neurons in the SCN.<sup>93</sup> Also sleep-wake distribution in hibernating ground squirrels did not show a circadian modulation.<sup>94</sup> In contrast, responses to, for instance, sleep deprivation, temperature changes, and other homeostatic regulatory processes, are still functioning.<sup>95-99</sup> Under certain circumstances a small circadian modulation of body temperature can be observed during hibernation;<sup>100</sup> however, we may conclude that the contribution of the circadian clock is reduced whereas homeostatic regulation seems to be virtually identical to its regulation outside the hibernation season.

## THERMOREGULATION AND METABOLIC RATE REDUCTION

The mechanism by which the animals reach the reduction in metabolic rate is still controversial. The traditional view was that metabolic rate falls as body temperature decreased at torpor entry. The  $Q_{10}$  of metabolic rate between euthermia and torpor is often close to 2, which is typical for biochemical processes;<sup>77</sup> therefore, the reduction in metabolic rate seems to be explained solely by the temperature effect on biochemical processes in the body.<sup>101,102</sup>

However,  $Q_{10}$  values above 3 for metabolic rate have been observed during torpor entry and during torpor at relatively high temperatures. It was proposed that an additional physiological inhibition must be involved in the reduction of metabolic rate.<sup>103,104</sup> Metabolic rate is down regulated before torpor entry, and the decrease in body temperature is the consequence and not the cause of the metabolic rate reduction.<sup>105-107</sup> As an alternative hypothesis it was proposed that metabolic rate is a function of the difference between ambient temperature and body temperature, similar as during euthermia.<sup>105</sup> As this difference is generally very small during torpor, metabolic rate is equally reduced.

Inhibition of metabolic rate during torpor may be caused by reduced pH, which slows down metabolic processes.<sup>108</sup> In hibernating ground squirrels the respiratory quotient (RQ) drops during entrance into torpor and rises during subsequent arousal, suggesting CO<sub>2</sub> storage, which may result in decreased pH. In contrast, in Djungarian hamsters, which display daily torpor, RQ increases during entrance into torpor and decreases before emergence from torpor. Changes in enzyme activity are other candidates for metabolic rate reduction. Mitochondrial respiration is reduced by 50% during torpor in hibernating ground squirrels, compared with euthermic individuals.

The previous data support the notion that the mechanism of metabolic rate reduction differs between hibernators and animals that use daily torpor.<sup>108</sup> The reduction in metabolic rate in animals who display daily torpor is largely determined by the decrease in body temperature, whereas hibernators seem to apply some kind of extra reduction in metabolic rate.

For some essential, but unknown reason, deep torpor in hibernators is interrupted on a regular basis by short (<24 hours) euthermic periods.<sup>109,110</sup> Above 0° C body temperature, torpor bout length correlates negatively with ambient temperature,<sup>111</sup> and metabolic rate depends on ambient temperature and, therefore, body temperature. The timing of the euthermic period (also called arousal)



correlates with the ambient temperature and the metabolic rate of the animal during the preceding hibernation bout.

More recent experiments indicate that the arousal is probably not induced by a process accumulating in the course of a multiday torpor bout, but that there exists a separate arousal process of which the onset is more susceptible at higher body or ambient temperatures.<sup>112</sup> Although the mechanism of the arousal is not known, it appears to be totally endogenous in its origin.

The question of the reason for the arousal is important. The function of hibernation is energy conservation, and energy expenditure during the hibernation season is reduced to less than 15% of what the animals would have expended if they remained euthermic throughout the winter season.<sup>90</sup> However, there is still room for improvement, because the energetic costs of the periodic arousals constitute 64% to 90% of the total energy expenditure during the hibernation season.<sup>90,113,114</sup> It has been proposed that arousals are required to eliminate metabolic waste products, to replenish blood glucose levels, or to restore cellular electrolyte balance. All these hypothesis have not survived critical experimental testing.<sup>115</sup> Based on EEG observations it was proposed that animals terminate torpor and return to euthermia to restore a sleep debt.<sup>116,117</sup> Non-REM sleep was deepest at the beginning of a euthermic period and most of the euthermic period was spent in sleep. The putative restorative function of NREM sleep was thought to be incompatible with torpor.

#### TORPOR AND SLEEP

Animals in torpor appear to be sleeping. They remain in their nest in a sleeplike posture with elevated arousal thresholds. Based on several behavioral and physiological findings it is generally accepted that torpor has evolved as an extension of sleep. Analysis of the EEG when animals enter torpor shows that rodents are mainly in NREM sleep and that REM sleep is reduced or not present.<sup>118,119</sup> Recordings of neuronal activity in the hypothalamus of hibernators with brain temperatures between 10° and 20° C indicate that these animals keep alternating between long NREM sleep bouts and short waking bouts.<sup>120</sup> Below 10° C it is not possible to determine vigilance states with electrophysiological methods.<sup>120</sup> These findings supported the hypothesis that NREM sleep is an adaptive behavior for energy conservation, which function is strengthened during torpor.<sup>12,92,121</sup>

However, when the animals subsequently emerge from torpor they immediately enter deep NREM sleep irrespective of whether the animals emerge from deep hibernation<sup>116,117</sup> or daily torpor.<sup>119</sup> This observation suggested that during deep torpor the function of sleep cannot be fulfilled completely, and animals have to return to euthermia to recover from a sleep deprivation incurred during the hypothermic state. In the Djungarian hamster, the hypothesis was confirmed by combining daily torpor with sleep deprivation experiments.<sup>95</sup> In contrast, similar experiments in hibernating ground squirrels resulted in rejection of the sleep deprivation hypothesis.<sup>97,98</sup>

There appear to be fundamental differences between animals who display daily torpor and hibernating animals that display multiple-day torpor bouts. The mechanism of metabolic rate reduction seems to differ.<sup>108</sup> Another fun-

damental difference between the two groups of animals is the effect of torpor on subsequent sleep. In hibernating animals who display deep torpor, such as ground squirrels or hamsters, regulation of temperature and sleep seems to be reduced to a level that currently cannot be measured reliably. In contrast, animals who display daily torpor appear to make use of the same processes, although applied in an extreme way, which reduces body temperature at the onset of sleep in humans. This latter similarity may provide an opportunity to investigate the relationship between sleep and body temperature with much larger variability.

#### ❖ Clinical Pearl

Humans with cold hands and feet are predisposed for difficulties initiating sleep. Better knowledge about sleep thermophysiology may help to develop evidence-based thermal interventions to alleviate sleep disturbances and to manage certain aspects of sleep and alertness problems in the general population. Therefore, to assess dysfunctional thermoregulation, clinicians can use objective skin temperature measurements in conjunction with patient self reports about thermal discomfort (e.g., sensation of cold hands and feet) to diagnose, monitor, and advise patients on their sleep disturbances or thermal discomfort-related complaints.

#### REFERENCES

1. Siegel JM. Do all animals sleep? *Trends Neurosci* 2008;31:208-213.
2. Siegel JM. Clues to the functions of mammalian sleep. *Nature* 2005;437:1264-1271.
3. Kräuchi K. The thermophysiological cascade leading to sleep initiation in relation to phase of entrainment. *Sleep Med Rev* 2007;11:439-451.
4. Mekjavic IB, Eiken O. Contribution of thermal and nonthermal factors to the regulation of body temperature in humans. *J Appl Physiol* 2006;100:2065-2072.
5. Tayefeh F, Plattner O, Sessler DI, et al. Circadian changes in the sweating-to-vasoconstriction interthreshold range. *Pflügers Arch* 1998;453:402-406.
6. Moore RY, Danchenko RL. Paraventricular-subparaventricular hypothalamic lesions selectively affect circadian function. *Chronobiol Int* 2002;19:345-360.
7. Mrosovsky N. Masking: history, definitions, and measurement. *Chronobiol Int* 1999;16:415-429.
8. Kräuchi K, Wirz-Justice A. Circadian rhythm of heat production, heart rate, and skin and core temperature under unmasking conditions in men. *Am J Physiol* 1994;267:R819-R829.
9. Kellogg DL Jr. In vivo mechanisms of cutaneous vasodilation and vasoconstriction in humans during thermoregulatory challenges. *J Appl Physiol* 2006;100:1709-1718.
10. Kräuchi K, Knoblauch V, Wirz-Justice A, et al. Challenging the sleep homeostat does not influence the thermoregulatory system in men: evidence from a nap vs. sleep-deprivation study. *Am J Physiol Regul Integr Comp Physiol* 2006;290:R1052-R1061.
11. Kräuchi K, Cajochen C, Pache M, et al. Thermoregulatory effects of melatonin in relation to sleepiness. *Chronobiol Int* 2006;23:475-484.
12. Berger RJ. Slow wave sleep, shallow torpor and hibernation: homologous states of diminished metabolism and body temperature. *Biol Psychol* 1984;19:305-326.
13. Horne JA. Why sleep? *Biologist* 2002;49:213-216.
14. Horne J. Human slow-wave sleep: a review and appraisal of recent finding, with implications for sleep functions, and psychiatric illness. *Experientia* 1992;48:941-954.

15. Fontvieille AM, Rising R, Spraul M, et al. Relationship between sleep stages and metabolic rate in humans. *Am J Physiol* 1994; 267:E732-E737.
16. Bach V, Telliez F, Libert JP. The interaction between sleep and thermoregulation in adults and neonates. *Sleep Med Rev* 2002; 6:481-492.
17. Kräuchi K, Cajochen C, Wirz-Justice A. A relationship between heat loss and sleepiness: effects of postural change and melatonin administration. *J Appl Physiol* 1997;83:134-139.
18. Kräuchi K. The human sleep-wake cycle reconsidered from a thermoregulatory point of view. *Physiol Behav* 2007;90: 236-245.
19. Geschickter EH, Andrews PA, Bullard RW. Nocturnal body temperature regulation in man: a rationale for sweating in sleep. *J Appl Physiol* 1966;630:623-630.
20. Sindrup JH, Kastrup J, Jorgensen B, et al. Nocturnal variations in subcutaneous blood flow rate in lower leg of normal human subjects. *Am J Physiol* 1991;260:H480-H485.
21. Kräuchi K, Cajochen C, Werth E, et al. Functional link between distal vasodilation and sleep-onset latency? *Am J Physiol Regul Integr Comp Physiol* 2000;278:R741-R748.
22. Barrett J, Lack L, Morris M. The sleep-evoked decrease of body temperature. *Sleep* 1993;16:93-99.
23. Muzet A, Libert J-P, Candau V. Ambient temperature and human sleep. *Experientia* 1984;40:425-429.
24. Kräuchi K, Cajochen C, Wirz-Justice A. Waking up properly: is there a role of thermoregulation in sleep inertia? *J Sleep Res* 2004;13:121-127.
25. Kräuchi K, Fontana P, Gasio P, et al. Cold extremities and difficulties initiating sleep: evidence of co-morbidity from a random sample of a Swiss urban population. *J Sleep Res* 2008;17:420-426.
26. Vollenweider S, Wirz-Justice A, Flammer J, et al. Chronobiological characterization of women with primary vasospastic syndrome: body heat loss capacity in relation to sleep initiation and phase of entrainment. *Am J Physiol Regul Integr Comp Physiol* 2008; 294:R630-R638.
27. van den Heuvel C, Ferguson S, Dawson D. Attenuated thermoregulatory response to mild thermal challenge in subjects with sleep-onset insomnia. *Sleep* 2006;29:1174-1180.
28. Gilbert SS, Van den Heuvel CJ, Ferguson SA, et al. Thermoregulation as a sleep signalling system. *Sleep Med Rev* 2004;8:81-93.
29. Recordati G. A thermodynamic model of the sympathetic and parasympathetic nervous systems. *Auton Neurosci* 2003;103:1-12.
30. Sarang PS, Telles S. Oxygen consumption and respiration during and after yoga relaxation techniques. *Appl Psychophysiol Biofeedback* 2006;31:143-153.
31. Kräuchi K, Cajochen C, Werth E, et al. Warm feet promote the rapid onset of sleep. *Nature* 1999;401(6748):36-37.
32. Dijk DJ, Czeisler CA. Body temperature is elevated during the rebound of slow-wave sleep following 40-h of sleep deprivation on a constant routine. *J Sleep Res* 1993;2:117-120.
33. Cajochen C, Kräuchi K, Wirz-Justice A. Dynamics of skin and core body temperature and heart rate in human sleep after a single administration of melatonin. *J Sleep Res* 1996;5(Suppl. 1):26.
34. Parmeggiani PL. REM sleep related increase in brain temperature: a physiologic problem. *Arch Ital Biol* 2007;145:13-21.
35. Landolt HP, Moser S, Wieser HG, et al. Intracranial temperature across 24-hour sleep-wake cycles in humans. *Neuro Report* 1995; 6:913-917.
36. Kawamura H, Sawyer CH. Elevation in brain temperature during paradoxical sleep. *Science* 1965;150:912-913.
37. Deboer T, Franken P, Tobler I. Sleep and cortical temperature in the Djungarian hamster under baseline conditions and after sleep deprivation. *J Comp Physiol A* 1994;174:145-155.
38. Alfvöldi P, Rubicssek G, Cserni G, et al. Brain and core temperatures and peripheral vasomotion during sleep and wakefulness at various ambient temperatures in the rat. *Pflügers Arch* 1990;417:336-341.
39. Franken P, Tobler I, Borbely AA. Sleep and waking have a major effect on the 24-hr rhythm of cortical temperature in the rat. *J Biol Rhythms* 1992;7:341-352.
40. Baker FC, Angara C, Szymusiak R, et al. Persistence of sleep-temperature coupling after suprachiasmatic nuclei lesions in rats. *Am J Physiol Regul Integr Comp Physiol* 2005;289: R827-R838.
41. Campbell SS, Broughton RJ. Rapid decline in body temperature before sleep: fluffing the physiological pillow? *Chronobiol Int* 1994;11:126-131.
42. Zully J. Distribution of REM sleep in entrained 24 hour and free-running sleep-wake cycles. *Sleep* 1980;2:377-389.
43. Lack LC, Gradisar M, Van Someren EJW, et al. The relationship between insomnia and body temperatures. *Sleep Med Rev* 2008; 12:307-317.
44. Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci* 1995;15:3526-3538.
45. Lavie P. Melatonin: role in gating nocturnal rise in sleep propensity. *J Biol Rhythms* 1997;12:657-665.
46. Rajaratnam SMW, Middleton B, Stone BM, et al. Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities in humans. *J Physiol* 2004;561:339-351.
47. Liao W-C. Effects of passive body heating on body temperature and sleep regulation in the elderly: a systematic review. *Int J Nursing Stud* 2002;39:803-810.
48. Buguet A. Sleep under extreme environments: effects of heat and cold exposure, altitude, hyperbaric pressure and microgravity in space. *J Neurological Sci* 2007;262:145-152.
49. Heller HC, Edgar DM, Grahn DA, et al. Sleep, thermoregulation, and circadian rhythms. In: Fregly MJ, editor. *Handbook of Physiology*, sect 4: environmental physiology. New York: Oxford University Press; 1996. p. 1361-1374.
50. Hammel HT, Elsner RW, Le Messurier DH, et al. Thermal and metabolic responses of the Australian aborigine exposed to moderate cold in summer. *J Appl Physiol* 1959;14:605-615.
51. Lange Andersen K, Loyning Y, Nelms JD, et al. Metabolic and thermal response to a moderate cold exposure in nomadic Laps. *J Physiol (London)* 1960;15:649-653.
52. Dewasmes G, Signoret P, Nicolas A, et al. Advances of human core temperature minimum and maximal paradoxical sleep propensity by ambient thermal transients. *Neurosci Lett* 1996;215: 25-28.
53. Togo F, Aizawa S, Arai J, et al. Influence on human sleep patterns of lowering and delaying the minimum core body temperature by slow changes in the thermal environment. *Sleep* 2007;30: 797-802.
54. Marino F, Booth J. Whole body cooling by immersion in water at moderate temperatures. *J Sci Med Sport* 1998;1:73-82.
55. Dorsey CM, Teicher MH, Cohen-Zion M, et al. Core body temperature and sleep of older female insomniacs before and after passive body heating. *Sleep* 1999;22:891-898.
56. Sung E-J, Tochihara Y. Effects of bathing and hot footbath on sleep in winter. *J Physiol Anthropol* 2000;19:21-27.
57. Liao WC, Chiu MJ, Landis CA. A warm footbath before bedtime and sleep in older Taiwanese with sleep disturbance. *Res Nurs Health* 2008;31:514-528.
58. Okamoto-Mizuno K, Tsuzuki K, Ohshiro Y, et al. Effects of an electric blanket on sleep stages and body temperature in young men. *Ergonomics* 2005;48:749-757.
59. Raymann RJ, Swaab DF, Van Someren EJ. Skin deep: enhanced sleep depth by cutaneous temperature manipulation. *Brain* 2008; 131:500-513.
60. Fronczek R, Overeem S, Lammers GJ, et al. Altered skin-temperature regulation in narcolepsy relates to sleep propensity. *Sleep* 2006;29:1444-1449.
61. Raymann RJ, Swaab DF, Van Someren EJ. Skin temperature and sleep-onset latency: changes with age and insomnia. *Physiol Behav* 2007;90:257-266.
62. Driver HS, Taylor SR. Exercise and sleep. *Sleep Med Rev* 2000;4:387-402.
63. Atkinson G, Fullick S, Grindley C, et al. Exercise, energy balance and the shift worker. *Sports Med* 2008;38:671-685.
64. Hague JFE, Gilbert SS, Burgess HJ, et al. A sedentary day: effects on subsequent sleep and body temperatures in trained athletes. *Physiol Behav* 2002;6869:1-7.
65. Van Someren EJW. Mechanisms and functions of coupling between sleep and temperature rhythms. *Prog Brain Res* 2006;153: 309-324.

66. McGinty D, Szymusiak R. Keeping cool: a hypothesis about the mechanisms and functions of slow-wave sleep. *Trends Neurosci* 1990;13:480-487.
67. Valatx JL, Roussel B, Cure M. Sleep and cerebral temperature in rat during chronic heat exposure. *Brain Res* 1973;55:107-122.
68. Deboer T, Tobler I. Shortening of the photoperiod affects sleep distribution, EEG and cortical temperature in the Djungarian hamster. *J Comp Physiol A* 1996;179:483-492.
69. Amici R, Cerri M, Ocampo-Garces A, et al. Cold exposure and sleep in the rat: REM sleep homeostasis and body size. *Sleep* 2008;31:708-715.
70. Amici R, Zamboni G, Perez E, et al. Pattern of desynchronized sleep during deprivation and recovery induced in the rat by changes in ambient temperature. *J Sleep Res* 1994;3:250-256.
71. Morairty SR, Szymusiak R, Thomson D, et al. Selective increases in non-rapid eye movement sleep following whole body heating in rats. *Brain Res* 1993;617:10-16.
72. Gao BO, Franken P, Tobler I, et al. Effect of elevated ambient temperature on sleep, EEG spectra, and brain temperature in the rat. *Am J Physiol* 1995;268:R1365-R1373.
73. Obal F Jr, Alfoldi P, Rubicsek G. Promotion of sleep by heat in young rats. *Pflügers Arch* 1995;430:729-738.
74. McGinty D, Szymusiak R, Thomson D. Preoptic/anterior hypothalamic warming increases EEG delta frequency activity within non-rapid eye movement sleep. *Brain Res* 1994;667:273-277.
75. Franken P, Dijk DJ, Tobler I, et al. Sleep deprivation in rats: effects on EEG power spectra, vigilance states, and cortical temperature. *Am J Physiol* 1991;261:R198-R208.
76. Tobler I, Franken P, Gao B, et al. Sleep deprivation in the rat at different ambient temperatures: effect on sleep, EEG spectra and brain temperature. *Arch Ital Biol* 1994;132:39-52.
77. Deboer T. Brain temperature dependent changes in the electroencephalogram power spectrum of humans and animals. *J Sleep Res* 1998;7:254-262.
78. Deboer T, Tobler I. Temperature dependence of EEG frequencies during natural hypothermia. *Brain Res* 1995;670:153-156.
79. Deboer T. Electroencephalogram theta frequency changes in parallel with euthermic brain temperature. *Brain Res* 2002;930:212-215.
80. Miller JD, Cao VH, Heller HC. Thermal effects on neuronal activity in suprachiasmatic nuclei of hibernators and nonhibernators. *Am J Physiol* 1994;266:R1259-R1266.
81. Daniel EE, Boddy G, Bong A, et al. A new model of pacing in the mouse intestine. *Am J Physiol Gastrointest Liver Physiol* 2004;286:G253-G262.
82. Eisenman JS, Edinger HM, Barker JL, et al. Neuronal thermosensitivity. *Science* 1971;172:1360-1362.
83. Boulant JA. Cellular mechanisms of neuronal thermosensitivity. *J Therm Biol* 1999;24:333-338.
84. Alam N, Szymusiak R, McGinty D. Local preoptic/anterior hypothalamic warming alters spontaneous and evoked neuronal activity in the magno-cellular basal forebrain. *Brain Res* 1995;696:221-230.
85. Alam MN, McGinty D, Szymusiak R. Thermosensitive neurons of the diagonal band in rats: relation to wakefulness and non-rapid eye movement sleep. *Brain Res* 1997;752:81-89.
86. Berner NJ, Heller HC. Does the preoptic anterior hypothalamus receive thermoafferent information? *Am J Physiol* 1998;274:R9-R18.
87. Kumar VM, Vetrivelan R, Mallick HN. Noradrenergic afferents and receptors in the medial preoptic area: neuroanatomical and neurochemical links between the regulation of sleep and body temperature. *Neurochem Int* 2007;50:783-790.
88. Geiser F, Ruf T. Hibernation versus daily torpor in mammals and birds: physiological variables and classification of torpor patterns. *Physiol Zool* 1995;68:935-966.
89. Barnes BM. Freeze avoidance in a mammal: body temperatures below 0 degree C in an Arctic hibernator. *Science* 1989;244:1593-1595.
90. Wang LCH. Time pattern and metabolic rates of natural torpor in the Richardson's ground squirrel. *Can J Zool* 1978;57:149-155.
91. Berger RJ. Comparative aspects of energy metabolism, body temperature and sleep. *Acta Physiol Scand* 1988;133:21-27.
92. Heller HC. Sleep and hypometabolism. *Can J Zool* 1988;66:61-69.
93. Hut RA, Van der Zee EA, Jansen K, et al. Gradual reappearance of post-hibernation circadian rhythmicity correlates with numbers of vasopressin-containing neurons in the suprachiasmatic nuclei of European ground squirrels. *J Comp Physiol* 2002;172:59-70.
94. Larkin JE, Franken P, Heller HC. Loss of circadian organization of sleep and wakefulness during hibernation. *Am J Physiol Regul Integr Comp Physiol* 2002;282:R1086-R1095.
95. Deboer T, Tobler I. Slow waves in the sleep electroencephalogram after daily torpor are homeostatically regulated. *Neuroreport* 2000;11:881-885.
96. Deboer T, Tobler I. Sleep regulation in the Djungarian hamster: comparison of the dynamics leading to the slow-wave activity increase after sleep deprivation and daily torpor. *Sleep* 2003;26:567-572.
97. Strijkstra AM, Daan S. Dissimilarity of slow-wave activity enhancement by torpor and sleep deprivation in a hibernator. *Am J Physiol* 1998;275:R1110-R1117.
98. Larkin JE, Heller CH. The disappearing slow wave activity of hibernators. *Sleep Res Online* 1998;1:96-101.
99. Lyman CP, Willis JC, Malan A, et al. Hibernation and torpor in mammals and birds. New York: Academic; 1982.
100. Ruby NF, Dark J, Burns DE, et al. The suprachiasmatic nucleus is essential for circadian body temperature rhythms in hibernating ground squirrels. *J Neurosci* 2002;22:357-364.
101. Guppy M, Withers P. Metabolic depression in animals: physiological perspectives and biochemical generalizations. *Biol Rev Camb Philos Soc* 1999;74:1-40.
102. Snapp BD, Heller CH. Suppression of metabolism during hibernation in ground squirrels (*Citellus lateralis*). *Physiol Zool* 1981;54:297-307.
103. Geiser F. Reduction of metabolism during hibernation and daily torpor in mammals and birds: temperature effect or physiological inhibition? *J Comp Physiol B* 1988;158:25-37.
104. Storey KB, Storey JM. Metabolic rate depression and biochemical adaptation in anaerobiosis, hibernation and estivation. *Q Rev Biol* 1990;65:145-174.
105. Heldmaier G, Ruf T. Body temperature and metabolic rate during natural hypothermia in endotherms. *J Comp Physiol B* 1992;162:696-706.
106. Heldmaier G, Steiger R, Ruf T. Suppression of metabolic rate in hibernation. In: Carey C, Florant GL, Wunder BA, Horwitz B, editors. *Life in the cold*. Boulder, Colo: Westview; 1993.
107. Nicol S, Andersen NA, Mesch U. Metabolic rate and ventilatory pattern in the echidna during hibernation and arousal. In: Augee ML, editor. *Platypus and echidnas*. Sydney: Royal Zool Soc NSW; 1992.
108. Geiser F. Metabolic rate and body temperature reduction during hibernation and daily torpor. *Annu Rev Physiol* 2004;66:239-274.
109. French AR. Allometries of the durations of torpid and euthermic intervals during mammalian hibernation: a test of the theory of metabolic control of the timing of changes in body temperature. *J Comp Physiol B* 1985;156:13-19.
110. Barnes BM, Kretzmann M, Licht P, et al. The influence of hibernation on testis growth and spermatogenesis in the golden-mantled ground squirrel, *Spermophilus lateralis*. *Biol Reprod* 1986;35:1289-1297.
111. Geiser F, Kenagy GJ. Torpor duration in relation to temperature and metabolism in hibernating ground squirrels. *Physiol Zool* 1988;61:442-449.
112. Strijkstra AM, Hut RA, Daan S. Does the timing mechanism of periodic euthermia in deep hibernation depend on its homeostatic need? In: Lovegrove BG, McKechnie AE, editors. *Hypometabolism in animals: torpor, hibernation and cryobiology*. Pietermaritzburg: University of KwaZuluNatal; 2008. p. 157-162.
113. Kayser C. L'hibernation des mammifères. *Annee Biol* 1953;29:109-150.
114. Daan S. Activity during natural hibernation in three species of vespertilionid bats. *Neth J Zool* 1973;23:1-71.
115. Willis JC. The mystery of the periodic arousal. In: Lyman CP, Willis JC, Malan A, Wang LCH, editors. *Hibernation and torpor*

- in mammals and birds. New York: Academic Press; 1982. p. 92-103.
116. Daan S, Barnes BM, Strijkstra AM. Warming up for sleep? Ground squirrels sleep during arousals from hibernation. *Neurosci Lett* 1991;128:265-268.
  117. Trachsel L, Edgar DM, Heller HC. Are ground squirrels sleep deprived during hibernation? *Am J Physiol* 1991;260:R1123-R1129.
  118. Walker JM, Garber A, Berger RJ, et al. Sleep and estivation (shallow torpor): continuous processes of energy conservation. *Science* 1979;204:1098-1100.
  119. Deboer T, Tobler I. Sleep EEG after daily torpor in the Djungarian hamster: similarity to the effect of sleep deprivation. *Neurosci Lett* 1994;166:35-38.
  120. Krilowicz BL, Glotzbach SF, Heller HC. Neuronal activity during sleep and complete bouts of hibernation. *Am J Physiol* 1988;255:R1008-R1019.
  121. Obal F Jr, Rubicsek G, Alfoldi P, et al. Changes in the brain and core temperatures in relation to the various arousal states in rats in the light and dark periods of the day. *Pflügers Arch* 1985; 404:73-79.