RESEARCH ARTICLE

Sleep during an Antarctic summer expedition: new light on “polar insomnia”

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Pattyn N, Mairesse O, Cortoos A, Marcoen N, Neyt X, Meeusen R. Sleep during an Antarctic summer expedition: new light on “polar insomnia”. J Appl Physiol 122: 788–794, 2017. First published January 12, 2017; doi:10.1152/japplphysiol.00606.2016.—Sleep complaints are consistenly cited as the most prominent health and well-being problem in Arctic and Antarctic expeditions, without clear evidence to identify the causal mechanisms. The present investigation aimed at studying sleep and determining circadian regulation and mood during a 4-mo Antarctic summer expedition. All data collection was performed during the continuous illumination of the Antarctic summer. After an habituation night and acclimatization to the environment (3 wk), ambulatory polysomnography (PSG) was performed in 21 healthy male subjects, free of medication. An 18-h profile (saliva sampling every 2 h) of cortisol and melatonin was assessed. Mood, sleepiness, and subjective sleep quality were assessed, and the psychomotor vigilance task was administered. PSG showed, in addition to high sleep fragmentation, a major decrease in slow-wave sleep (SWS) and an increase in stage R sleep. Furthermore, the ultradian rhythmicity of sleep was altered, with SWS occurring mainly at the end of the night and stage R sleep at the beginning. Cortisol secretion profiles were normal; melatonin secretion, however, showed a severe phase delay. There were no mood alterations according to the Profile of Mood States scores, but the psychomotor vigilance test showed an impaired vigilance performance. These results confirm previous reports on “polar insomnia”, the decrease in SWS, and present novel insight, the relationship between a phase-shifted melatonin rhythm, thus desynchronization of the rhythm of several physiological subsystems from the sleep-wake rhythm can be even more important (3, 25). Indeed, the loss of photoperiod, through constant illumination during summer and constant darkness during winter, has repeatedly been shown to have a disturbing effect on hormonal regulation (22) and more specifically with regard to sleep regulation, on melatonin suppression and desynchronization (19, 23).

The absence of this circadian fluctuation in exposure to daylight during summer and winter in Antarctica may thus result in sleep problems and sleep-wake rhythm disturbances (23), despite the fact that some authors (38) did not evidence a relationship between a phase-shifted melatonin rhythm, thus being disturbed by the absence of photoperiod, and a stable rest-activity rhythm (measured through actigraphy), showing no desynchronization compared with baseline measures. Another study investigating eight men over-wintering in Antarctica showed an increase in the number of sleep episodes, accompanied with a delay in sleep phase in the winter compared with the summer period (31). Some even observed larger effects of over-wintering on sleep-wake rhythm in four individuals, since a free-run of this rhythm developed during winter (18). At first glance, these findings may seem contradictory with each other, unless the role of social zeitgebers, in this case the work schedule, is taken into account. Indeed, the
phase of the sleep rhythm seemed unchanged during winter-over in comparison with summer (38), while the melatonin and core temperature rhythm were phase delayed by ~4.1 and 2 h, respectively. These authors thus concluded that the effects of the lack of photoperiod on the sleep-wake rhythm was counteracted by social time cues, that is, the work schedule, whereas the influence of the photoperiod was more dominant for the circadian rhythm in melatonin and core body temperature. Their conclusion is supported by other studies, varying the extent to which social time cues, such as a stringent work schedules, are imposed, and where the winter-over impact on the sleep-wake pattern varied accordingly. Indeed, in the data described earlier (18), participants had the opportunity to allow their rest-activity cycle to free run; whereas other authors (37) showed the difference between two cohorts (inhabitants of a village leading their normal lives vs. personnel from a military base following a strict social schedule).

The present study aimed at investigating the causal mechanisms subtending sleep complaints during an Antarctic summer expedition. This was the building expedition of a new station, where the participants were sleeping in tents, thus being maximally exposed to the constant illumination of the Antarctic summer. We aimed to uncover the relationship between objective sleep-wake cycle, as measured through polysomnography, mood, and circadian sleep-wake regulation through cortisol and melatonin secretion.

METHODS

Procedure. The protocol was approved by the institutional review board of the Vrije Universiteit Brussels, and all participants gave written, informed consent. The investigation was conducted during one of the construction expeditons of the Belgian station in Antarctica (Princess Elisabeth; latitude 71°57’ S; longitude 23°20’ E; altitude 1,382 m, corrected equivalent of 1,800 m), during a summer campaign lasting for 4 mo. Recordings took place after an acclimatization period on site of 3 wk, and after an habituation night for the polysomnography. Monitoring took place on top of normal activities, meaning participants performed their usual daily duties and slept in their individual tents during the night. All recordings took place during the period of constant illumination. Light intensity on sunny days can exceed 40,000 lux outside (30). The tents in which participants were sleeping were made of bright yellow nylon, meaning they allowed daylight through. However, none of the participants used sleep masks, either during the study night or otherwise.

On the night of their recording, participants would come to the surgery to be kitted out, then they came back to get changed and visit the sanitary container, then they came back to the surgery to be kitted out, then they had the opportunity to allow daylight through. However, none of the participants used sleep masks, either during the study night or otherwise.

On the night of their recording, participants would come to the surgery to be kitted out and fill in the questionnaires. This would occur right before retreating to their individual tents to go to bed, which was always between 2230 and 2330. The morning after, they would again come to the surgery to be kitted out, then they had the opportunity to get changed and visit the sanitary container, then they came back to fill in the questionnaires and perform the psychomotor vigilance task (which would thus take place 45 min after waking up). The morning session always occurred between 0700 and 0730. These timings were followed by the whole crew, as the daily life followed a regular schedule with regard to working hours and meal times, apart from Saturday night and Sundays, which were the rest periods. For this reasons, no PSG was conducted on these days/nights. Coffee, nicotine, and alcohol use were not restricted due to the protocol; however, a “two cans rule” was enforced on station with regard to alcohol consumption.

Analysis. Due to the heterogeneity of the crew in terms of origin, and availability outside of the deployment period, it was not possible to obtain baseline measurements or post hoc baselines in the laboratory. Therefore, we used a group of matched controls [age, sex, body mass index (BMI)] for a between-group analysis of the polysomnography, Psychomotor Vigilance Test (PVT), and questionnaire data, based on an analysis of variance of the outcome variables with group as a single factor.

Participants. In the Antarctic group, 21 healthy, medication-free men, aged between 27 and 57 yr (mean age: 35 yr), agreed to participate in the present investigation. All were free of significant medical or psychiatric antecedents and had normal BMIs, comprised between 21 and 26 kg/m² (mean BMI: 23.2 kg/m²). The good sleep control group consisted of 12 healthy, medication-free men, aged between 20 and 43 yr (mean age: 29 yr), with a BMI comprised between 20 and 26 kg/m² (mean BMI: 22.7 kg/m²), who were recorded after a habituation night in the sleep laboratory of the Vrije Universiteit Brussels. These participants followed a normal weekday schedule, none of them ever performed shift work, and all were selected based on normal Pittsburgh Sleep Quality Index scores and being self-reported “good sleepers”.

Saliva sampling. Saliva samples were collected in the Antarctic group only, using Sarstedt salivettes (51.1534). Participants were required to chew for 1 min on the untreated cotton swab. Sampling was performed every 2 h, according to the sampling quality requirements described by the manufacturer, during the waking time of the participants. Samples were frozen the same day, stored for 3 mo, including transport, at −20°, and analyzed after thawing and centrifugation using the Direct Saliva Melatonin RIA RK-DSM2 from Buhllmann for melatonin dosage and the GammaCoat Cortisol CA1549E from DiaSorin for cortisol determination.

Polysomnography. Ambulatory polysomnography was recorded using the LifeShirt device (VivoMetrics Inc.) with the BioSomnia add-on for sleep recordings. The recording montage consisted of one EEG channel (Oz-A1), one electrooculogram referenced to a single mastoid (right outer canthus), a bipolar submentalis electromyogram (EMG), a single-lead ECG, thoracic and abdominal respiration through inductive plethysmography, and pulse oximetry. The signals were recorded at a sampling rate of 500 Hz and digitally upsampled to 1 kHz. The EEG and electrooculogram signals were high-pass filtered at 0.5 Hz and low-pass filtered at 40 Hz; EMG channels were high-pass filtered at 5 Hz and low-pass filtered at 70 Hz; and ECG and respiration were low-pass filtered at 40 Hz. Because of the issues encountered with the equipment during the field study, the regular equipment from the sleep laboratory was used for the control study (Medatec B3IP). However, the data acquisition parameters (sampling frequency and filtering) were kept constant across groups. All data was scored in 30-s epochs according to the American Academy of Sleep Medicine scoring rules (2) by a trained specialist, who analyzed the whole data set. Outcome variables were total sleep time (TST); sleep onset latency (SOL), defined as the time between lying down to the first minute of stage 1 sleep; wake after sleep onset; sleep efficiency (SE); %SWS of the sleep period time (SPT); %stage R sleep of the SPT and sleep stages 1 and 2 sleep (S1–S2) of the SPT; stage R latency; and SWS latency. ECG and respiration data were visually inspected for artifacts; ectopic beats or erroneous R-wave detections were manually corrected (removal of erroneous detection/artifact, followed by a cubic spline interpolation; corrections < 1%).

Questionnaires. At night and in the morning, the Tension, Depression, Anger, Fatigue, and Vigor subscales (32 items) of the Profile of Mood States was administered in the native language of the participants (10, 36), as well as the Karolinska Sleepiness Scale (KSS) (13). In addition, participants were asked in the morning to evaluate their sleep quality on a scale from 1 to 10 and to fill in a sleep diary, as well as French and Dutch translations of the Self-Assessment of Sleep and Awakening Quality Scale (SSA) (27). The SSA data are only available for the Antarctic group.

Psychomotor vigilance task. The 10-min version of the PVT (9) was administered to participants in the morning after their polysomnography. The PVT was administered through a laptop, where participants had to press the mouse button to respond while holding the
mouse in their dominant hand. The organization of the morning session (taking off the ambulatory monitoring equipment, getting changed, and basic hygiene, and then questionnaires and PVT) ensured we would avoid sleep inertia confounding the PVT results.

RESULTS

Polysomnography. Out of 21 participants, only the data from 9 of them were suitable for sleep scoring due to technical difficulties encountered during the field polysomnographic monitoring. Indeed, the single EEG channel proved a major obstacle, for loss of one of its electrodes meant the impossibility to score sleep stages. The outcome variables for both the Antarctic group and the control group are summarized in Table 1. This covers only the neurological data; indeed, the cardiorespiratory and EMG data were analyzed to exclude sleep disorders (related to breathing or movement), but are not presented in this section.

Results clearly show worsened objective sleep parameters in the Antarctic group compared with the control group. Despite similar TST and decreased SOL, the Antarctic group shows a significantly reduced SE, due to a greater proportion of time spent awake after the first episode of sleep.

Compared with the control group, the sleep architecture of the participants in the Antarctic group is heavily disturbed. There is a major decrease in SWS in the Antarctica group, where it is more than halved, as well as a major increase in stage R sleep, which is more than doubled. Furthermore, the SWS latency shows that, unlike in normal sleep, in the Antarctica group, the deep sleep episodes occur after stage R sleep episodes, in the second half of the night.

Subjective sleep quality. As expected from previous research, participants in Antarctica rated their sleep as poor, and there is a highly significant difference between the control group and the Antarctic group. Furthermore, as shown by the Karolinska scores (Table 2), there is no restorative effect of the night on sleepiness scores: in the control group. We see the expected difference between evening and morning scores, whereas this trend is inverted in the Antarctica group.

Since the SSA data are only available for the Antarctica group, we only examined it for qualitative purposes. With regard to sleep quality, two questions showed a clear interpretative lead, and these were “Did you have trouble maintaining sleep?”, where 70% of participants answered “Moderately” to “A lot”; and “Did you experience your sleep as refreshing?”, where 70% of participants answered “No” to “A little.” Furthermore, participants reported having experienced a profound sleep (85% “Moderately” to “A lot”). With regard to awakening quality, the majority of participants reported feeling sated after getting up in the morning (70% “Moderately” to “A lot”). Furthermore, 75% reported feeling slowed down (“Moderately to “A lot”) and feeling their attention/concentration diminished (“Moderately to “A lot”). The questions targeting initiation of sleep, mood, and more somatic symptoms did not show any unusual responses.

Mood. The Antarctic group does not seem to experience adverse effects on mood from the deployment, quite the contrary: their Vigor scores are higher than those of the control group, despite this difference not reaching significance [F(1,21) = 3.3; P = 0.085]. The overall evening and morning scores in both groups only reveal the restorative effect of the night on the negative subscales (Table 3).

PVT. As shown in Fig. 1, the Antarctic group was severely impaired both for reaction times and lapses. For both variables, the difference was significant between both groups [reaction times: t(24) = 8.7; P < 0.001; lapses: t(24) = 2.9; P = 0.009].

Cortisol. Cortisol secretion retains a normal circadian pattern, as shown on Fig. 2. Peak cortisol values occur on average

Table 1. Summary of the polysomnographic data for the Antarctic group and the control group

<table>
<thead>
<tr>
<th></th>
<th>Good Sleeper Control Group (N = 12)</th>
<th>Antarctic Group (N = 9)</th>
<th>t</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SE, %</td>
<td>92.7 4.09</td>
<td>80.73 6.99</td>
<td>5.079</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TST, min</td>
<td>412.50 32.29</td>
<td>342.55 127.35</td>
<td>1.77</td>
<td>0.104</td>
</tr>
<tr>
<td>SOL, min</td>
<td>24.92 12.61</td>
<td>4.09 3.48</td>
<td>5.498</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WASO, %</td>
<td>5.00 4.25</td>
<td>19.52 7.37</td>
<td>5.783</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SWS, %</td>
<td>31.99 9.37</td>
<td>13.24 10.02</td>
<td>4.531</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LS, %</td>
<td>42.55 7.96</td>
<td>33.62 8.08</td>
<td>2.602</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>R, %</td>
<td>16.81 4.51</td>
<td>33.62 11.82</td>
<td>4.247</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>R latency, min</td>
<td>137.75 46.29</td>
<td>56.27 45.85</td>
<td>4.236</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SWS latency, min</td>
<td>33.92 13.26</td>
<td>148.22 96.12</td>
<td>-3.542</td>
<td>0.010</td>
</tr>
<tr>
<td>R-SWS, min</td>
<td>378.33 441.36</td>
<td>186.44 127.83</td>
<td>3.46</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

SE: sleep efficiency; TST: total sleep time; SOL: sleep onset latency; WASO: wake after sleep onset; SWS: slow-wave sleep; LS: light sleep = stages 1 and 2; R: stage R sleep = rapid eye movement sleep; R-SWS: latency between the first R episode and the first SWS episode.

Table 2. Summary of the subjective sleep assessment data for the Antarctic group and the control group

<table>
<thead>
<tr>
<th></th>
<th>Good Sleeper Control Group</th>
<th>Antarctic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>7.6</td>
<td>1.1</td>
</tr>
<tr>
<td>KSS evening</td>
<td>5.4</td>
<td>1.7</td>
</tr>
<tr>
<td>KSS morning</td>
<td>4.4</td>
<td>1.7</td>
</tr>
</tbody>
</table>

KSS, Karolinska Sleepiness Scale. Sleep quality was a score that participants had to rate from 1 to 10. Both groups were compared through an independent samples t-test for sleep quality (t = 5.5; P < 0.001) and with a mixed ANOVA with group as a between-subject factor and moment as a within-subject factor for the Karolinska scores. Neither group nor moment showed significant effects, but the interaction between group and moment was highly significant [F(1,32) = 14.2; P = 0.001].
around 7:47 AM, consistent to what is found in the literature regarding healthy subjects in normal circumstances (32, 33).

Melatonin. Figure 3 illustrates that the results for the melatonin secretion lack the usual dim light melatonin onset (20), since secretion does not increase during the last part of the sampling (until midnight). However, values for the morning samples, around 7:00 AM, still show serum elevations compatible with an important phase delay in the secretion (1).

We observe no statistical significant difference between peak secretion hours of melatonin and cortisol \[t(15) = -0.890, P = 0.388\].

DISCUSSION

The purpose of the present investigation was to investigate sleep architecture and sleep-wake regulation during an Antarctic summer expedition, in an attempt to clarify the mechanisms subtending the subjective complaints reported in the existing literature.

Our findings on subjective sleep quality confirm previous reports, being that participants in Antarctica consistently complain about poor sleep quality. Not only is the difference between the Antarctic group and the control group striking regarding healthy subjects in normal circumstances (32, 33).

Salivary cortisol

Fig. 2. Cortisol secretion pattern over an 18-h profile. The shaded area represents the measured peak of secretion in our sample.

Salivary melatonin

Fig. 3. Melatonin secretion pattern over a 20-h secretion profile. The shaded area represents the measured peak of secretion in our sample.

feeling slowed down, and having a diminished attention capacity. When looking at the PVT results, these are indeed compatible with poor sleep, being similar to results after 5 consecutive days of a partial sleep deprivation of 4 h sleep a night (34). However, when looking at the results from the Profile of Mood States, it is interesting to see that the Fatigue scores are not increased compared with the control group. Vigor scores are even higher, even if the difference does not reach significance. Furthermore, the overall mood of the Antarctic group was quite good, hence not affected either by the harsh environment or the poor sleep quality. Another potential explanation for the low fatigue ratings, despite the poor sleep quality, might be the effect of the continuous exposure to daylight, which could participate in the positive mood effect. It should be noted that most of the sources describing adverse mood effects in Antarctic expeditions (for a review, see Ref. 25) report investigations taking place over the course of an over-wintering, hence a much longer duration of isolation and confinement, including several weeks of exposure to complete darkness. Our results are from a summer expedition and show none of the previously described mood impairments, despite the presence of severe sleep disruption. As such, this disentangling is interesting for causal hypotheses with regard to the origins of either mood alterations and/or sleep disruptions during this type of expeditions.

When looking at the sleep architecture, it indeed shows severe disruption. The shortened SOL, despite the KSS evening scores not being high, suggests a state of partial sleep deprivation, where the exposure to the constant illumination might counteract sleepiness, but where this sleepiness emerges as soon as the individual is removed from the illumination. The combination of the shortened SOL, the decreased SE, and the increased wake after sleep onset shows this decreased SE is due to a higher sleep fragmentation. This pattern of results could be associated with a chronically nonrestorative sleep, causing participants to be sleep deprived, and thus exhibit shortened SOL. When examining the sleep architecture, one of the most significant findings is the decrease in SWS, which confirms previous findings (4, 26) and is consistent with the perception of a nonrestorative sleep. The decrease in SWS is not associated with an increase in light sleep, but to an increase in stage R sleep. Again, this is puzzling. The exposure to cold
could be one of the factors influencing the disruption in sleep architecture. Indeed, the individual tents in which participants slept were not heated and were well ventilated. However, none of the participants ever complained of cold during the night (the provided equipment was adequate for the experienced temperatures), nor of temperature being a factor of influence in sleep disruption. Furthermore, cold exposure decreases stage R sleep and not SWS (5). One might argue we have no data to assess the homeostatic pressure in the Antarctic group, and it has been hypothesized before that life on an Antarctic station may lead to less physical activity due to confinement (3). This might be the case for over-winterings; however, the present setting was a construction expedition, where all participants performed physical tasks. Hence a decreased homeostatic drive subtending the decreased SWS seems highly unlikely. Another puzzling finding in the sleep architecture is the disruption of the ultradian rhythm. Indeed, as shown by the SWS latency and the R latency, SWS tends to occur at the end of the night, whereas most of R sleep occurred at the beginning of the night, thus showing the inverse of the expected sleep structure.

Nowithstanding the extreme environment and the harsh circumstances, the secretion of cortisol showed no effect of stress whatsoever. Despite the fact that the secretion profile data we measured are incomplete (18 h instead of 24 h), they provide highly interesting information. Indeed, cortisol shows a preserved circadian profile and is highly synchronized among participants, whereas melatonin secretion shows a severe phase delay. The exact secretion onset and secretion peak of melatonin could not be determined due to methodological constraints. Indeed, with this being a building expedition where participation in the experiment was not allowed to infringe on usual operational duties, it was unrealistic to expect participants to agree to be woken up every two hours during their night rest. However, considering the secretion kinetics of melatonin (for a review, see Ref. 1), considering the secretion onset is not measured as late as midnight, and considering that we have an important residual level at 7:00 AM, we can conclude the secretion peak is delayed. The remarkably preserved cortisol secretion is similar to previous findings with regard to altered photoperiods (15, 37) and does not confirm the advanced morning cortisol rise in lengthened exposure to bright day light (35). In the present study, cortisol secretion can be related to the social schedule of the expedition crew. Indeed, there was a fixed daily schedule to which all participants had to adhere (wake-up time, meal times), hence creating a similar social time for the whole crew.

The phase delay of melatonin is not surprising in itself. Indeed, it confirms previous research from both Antarctica (1, 8, 11) and Scandinavia (29) showing a phase-delayed secretion in periods of constant illumination, with increased melatonin levels between 0000 and 0900. The fact that its secretion profile is considered to be a marker for the biological night (1, 28), and that, as such, melatonin has been termed “the darkness hormone” shows that, as has been repeatedly demonstrated, melatonin secretion is inhibited when exposed to constant daylight of very high intensity.

It seems that cortisol follows the social time, which was already suggested by previous research (37), but dissociates from melatonin, which is most sensitive to the photic input. Yoneyama et al. (38) have described several possible interac-

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left only 9 participants out of the 21 for the qualitative analysis of sleep. The recording montage for PSG was minimal, with only a single-lead occipital EEG, which also impairs the possibility to make definitive comments about SWS. The fact that our field setup only included a single EMG, placed on the chin, and not a leg EMG, does not allow us to rule out certain movement disorders, such as periodic limb movement disorder, in our participants. However, the sleep architecture we measured confirms previous reports on SWS decrease. Furthermore, the 18-h sampling for the hormonal profiles does not allow us to exactly determine the secretion peak for melatonin. Again, this methodological choice was guided by the operational conditions: the participants had highly demanding schedules during the day, and waking them every 2 h during their night rest for saliva sampling would have been unacceptable to them. Salivary melatonin was chosen instead of urinary melatonin because of the lack of sanitary installations: toilets were very rudimentary (a drum for the male participants to urinate in, and wooden cabinets to defecate in bin bags), with no heating, and no possibility for “comfortable” hand washing. Hence, the collection of 24-h urine would have been quite complicated (keeping the containers from repeated freezing and thawing) and unhygienic for the participants.

However, despite these limitations, it is our opinion that these results shed a new light on the mechanisms subtending “polar insomnia,” both in terms of sleep architecture and in terms of sleep-wake regulation. The sparse literature in this area does not allow yet the differentiation of the effects of Antarctic deployment in summer (constant illumination) and winter (constant darkness). The present results warrant the need for a repeated investigation in both summer and winter conditions.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
N.P., conceived and designed research; N.P. and N.M. performed experiments; N.P., O.M., and A.C. interpreted results of experiments; N.P. and O.M. prepared figures; N.P. and A.C. analyzed data; N.P., O.M., N.M., X.N., and R.M. contributed author(s).

REFERENCES


