Manipulation of skin temperature improves nocturnal sleep in narcolepsy

R Fronczek,[1,2] R J E M Raymann,[1] S Overeem,[2,3] N Romeijn,[1] J G van Dijk,[2] G J Lammers,[2] E J W Van Someren[1,4]

[1] Netherlands Institute for Neuroscience, Amsterdam, The Netherlands; [2] Department of Clinical Neurology and Neurophysiology, Leiden University Medical Center, Leiden, The Netherlands; [3] Center for Sleep–Wake Disorders "Kempenhaeghe," Heeze, The Netherlands; [4] Department of Clinical Neurophysiology, Neurology and Medical Psychology, VU University Medical Center, Amsterdam, The Netherlands

Correspondence to: Dr R Fronczek, Leiden University Medical Centre, Department of Neurology (K5Q), PO Box 9600, 2300 RC, Leiden, The Netherlands; r.fronczek@lumc.nl

Received 4 January 2008
Revised 21 May 2008
Accepted 1 June 2008
Published Online First 30 July 2008

ABSTRACT

Objective: Besides excessive daytime sleepiness, disturbed nocturnal sleep is a major complaint of patients with narcolepsy. Previously, alterations in skin temperature regulation in narcoleptic patients have been shown to be related to increased sleepiness. This study tests the hypothesis that direct control of nocturnal skin temperature might be applied to improve the disturbed sleep of narcoleptic patients.

Methods: Participants were eight patients (five males) diagnosed as having narcolepsy with cataplexy according to the ICSD-2 criteria, mean (SD) age 28.6 (6.4) years, range 18–35 years. During two nights, sleep was recorded polysomnographically while proximal and distal skin temperature were manipulated using a comfortable thermosuit that induced skin temperature to cycle slowly with an amplitude of only 0.4°C within the comfortable range normally observed during sleep. Logistic regression was used to evaluate the effect of skin temperature manipulation on the probability of occurrence of different sleep stages and nocturnal wakefulness.

Results: Proximal skin warming significantly suppressed wakefulness and enhanced slow wave sleep (SWS). In contrast, distal skin warming enhanced wakefulness and stage 1 sleep at the cost of SWS and REM sleep. The optimal combination of proximal skin warming and distal skin cooling led to a 160% increase in SWS, a 50% increase in REM sleep and a 68% decrease in wakefulness, compared with the least beneficial combination of proximal skin cooling and distal skin warming.

Interpretation: Subtle skin temperature manipulations under controlled conditions significantly improved the typical nocturnal sleep problems in narcolepsy.

The four classical symptoms of narcolepsy are excessive daytime sleepiness, cataplexy, hypnagogic hallucinations and sleep paralysis.[1] In recent years, disturbed nocturnal sleep has gained increasing attention as a fifth core symptom that severely affects quality of life.[1] Nocturnal polysomnography in patients with narcolepsy shows a fragmentation of the normal sleep pattern with frequent arousals and a decrease in slow wave sleep.[2–4] Several hypnotics, including sodium oxybate (gammahydroxybutyrate), are currently used to improve nocturnal sleep in narcolepsy.[5] Narcolepsy is caused by a loss of the neuropeptide hypocretin (orexin), a neurotransmitter that is produced by neurons in the lateral hypothalamus.[6 7]

There is a relation between sleep and both core body and skin temperature.[8 9] In everyday life and under laboratory conditions with a comfortable to warm environmental temperature, core body temperature is lower and the average skin temperature is higher during the night than during the day.[9 10] Sleep-onset latency is negatively correlated to the temperature of distal skin areas (hands and feet).[11] There seems to be a causal relation, since mild warming of the skin compromises sustained vigilance[12] and facilitates sleep initiation.[13] Moreover, mild active manipulation of the skin temperature within the comfortable and circadian range affects night-time sleep in healthy controls.[14]

In a previous study, we reported disturbances in skin-temperature regulation in narcolepsy.[15] Narcoleptic subjects showed a combination of a higher distal skin temperature and a lower proximal skin temperature, which in healthy subjects is associated with the process of falling asleep.[11] In a follow-up study, we were able to improve both daytime vigilance and maintenance of wakefulness by mild manipulation of skin temperature and core body temperature.[16] To test the hypothesis that manipulation of skin temperature might be applied to ameliorate the disturbed nocturnal sleep in narcolepsy as well, we performed subtle manipulations of proximal and distal skin temperature during two nocturnal sleep episodes in eight narcoleptic patients.

MATERIALS AND METHODS

Subjects

Eight narcoleptic patients (five males, 18–35 years of age; mean (SD): 28.6 (6.4) years) participated with informed consent. All suffered from excessive daytime sleepiness and typical cataplexy according to the ICSD-2 criteria for narcolepsy with cataplexy.[17] All subjects were free of medication, except for one female subject using oral contraceptives. All females participated between day 4 and day 12 of the menstrual cycle (mid-follicular phase or pseudo-follicular phase). All subjects participated in the summer season (July/August). The protocol was approved by the Medical Ethics Committees of the Academic Medical Center in Amsterdam and the Leiden University Medical Center. The same eight subjects were used in the aforementioned study, where both skin temperature and core body temperature were manipulated during daytime.[16]

Design

A previously described design was used to differentially manipulate proximal and distal skin temperature, and to determine the effects of these manipulations on sleep depth.[14] Subjects refrained from caffeine, alcohol and tobacco for 8 h before reporting at the sleep laboratory at 22:00. There they were prepared for polysomnography and fitted with a thermosuit. At midnight, lights were turned off, and subjects were allowed to sleep until

Table 1 Odds ratio (OR), CI and p value for the occurrence of each sleep state as modulated by the temperature of the thermosuit warming the distal ($T_{suit-dist}$) and proximal ($T_{suit-prox}$) skin (per 1°C)

	$T_{suit-prox}$		$T_{suit-dist}$	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Wake	0.81 (0.77 to 0.84)	<0.001	1.11 (1.06 to 1.16)	<0.001
S1	0.98 (0.93 to 1.03)	NS	1.22 (1.16 to 1.28)	<0.001
S2	1.02 (0.99 to 1.05)	NS	1.01 (0.98 to 1.04)	NS
SWS	1.23 (1.17 to 1.29)	<0.001	0.85 (0.81 to 0.89)	<0.001
REM	0.98 (0.93 to 1.03)	NS	0.87 (0.83 to 0.92)	<0.001

REM, rapid-eye-movement sleep; S1, stage 1 sleep; S2, stage 2 sleep; SWS, slow-wave sleep.

06:00. From 00:30 until 06:00, their proximal and distal skin temperatures were manipulated. After this, subjects slept one night at home, after which they returned for a second night in the sleep laboratory, during which the temperature manipulation sequence (see below) was inverted to that of the first night.

Temperature manipulations and measurement

Starting at 0:30, the temperature of the proximal skin ($T_{skin-prox}$) and the temperature of the distal skin ($T_{skin-dist}$) were differentially manipulated by slowly altering the temperature of the water that perfused the thermosuit (fig 1). The suit temperature (T_{suit}) stayed at constant plateaus of either 15 or 30 min with slow (15 min) transitions in between. The order of the sequences of skin temperature manipulations was different for each subject within its group and chosen in such a way that it resulted in an optimal uniform distribution of combinations of high and low $T_{suit-prox}$ and $T_{suit-dist}$ levels throughout the night over all subjects, that is at any time of night there was an equal proportion of "warm" and "cool" periods. T_{suit} cycled between 31.9 (0.1)°C (mean (SE)) in the "cool" and 34.8 (0.1)°C in the "warm" condition, as measured once per minute on the isolated inflow tubes at their connections with the thermosuit using PT100 thermistors (RTD-3-3105, Omega, Stanford). This range was specifically chosen to match the previously reported range of temperatures normally present in the bed microclimate.[18] The environmental temperature was kept at 21°C. Skin and core body temperature was recorded as described previously.[13]

Sleep recordings

Polysomnographic sleep recordings were performed according to standard procedures.[19] An experienced sleep technician blind to the temperature conditions scored sleep stages in 30-second epochs according to the Rechtschaffen and Kales criteria using Somnologica software.[20]

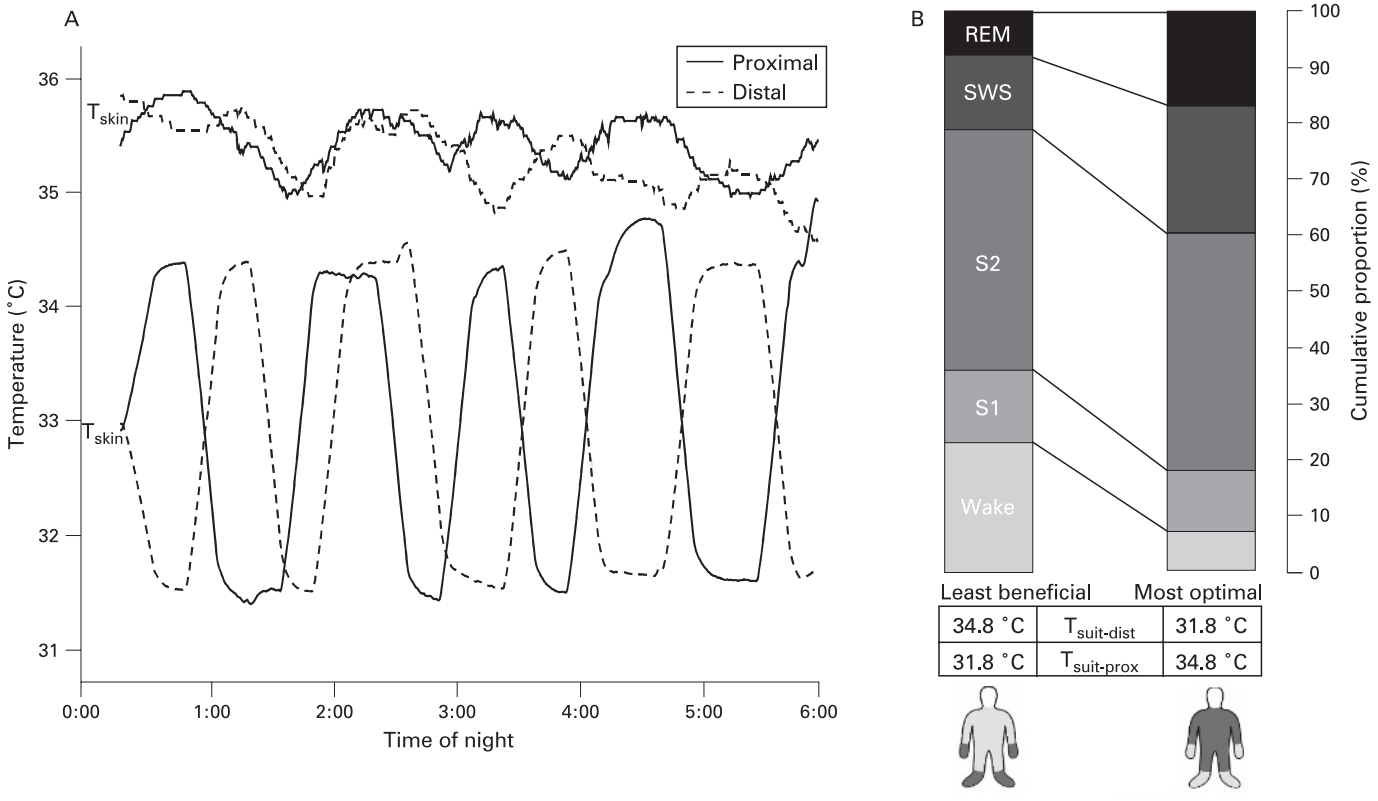

Figure 1 (A) Example of a temperature profile induced in one patient during a single night. The lower traces show the temperature of the proximal (solid line) and distal (dotted line) parts of the thermosuit. The upper traces show the actually induced proximal and distal skin temperatures. (B) Graphical representation of the proportion of the sleep stages during the optimal (distal cooling and proximal warming) and least beneficial (distal warming and proximal cooling) manipulation scheme. The proportions were derived in separate logistic regressions for each sleep stage. For graphical purposes only, the figure was rescaled to 100%. REM, rapid-eye-movement sleep; S1, stage 1 sleep; S2, stage 2 sleep; SWS, slow-wave sleep.

Statistical analysis

The main outcome measures of this study were the effects of proximal and distal skin warming or cooling on the odds ratios for the occurrence of each sleep stage (stage 1, stage 2, slow-wave sleep, REM sleep and wakefulness). Mixed effect (or multilevel) regression modelling was applied to account for the interdependency of the data points inherent to the hierarchical structure of the dataset: sleep epochs within nights within subjects (MLwiN software, Centre for Multilevel Modelling, Institute of Education, London).[21] The analyses included all epochs during the skin temperature cycles (from 00:30 until 6:00). To determine the effects of skin temperature manipulation on the probability of occurrence of each sleep stage or wakefulness, longitudinal multilevel logistic regressions were applied for each sleep stage classification, with the current presence or absence of that stage as dummy coded dichotomous dependent variable and $T_{suit\text{-}prox}$ and $T_{suit\text{-}dist}$ as predictor variables. Two-tailed significance levels were set at 0.05. For a graphical representation, odds ratios (OR) were translated into whole-night sleep stage probabilities for two conditions, reflecting the most and least profitable combination of upper (34.8 (0.1)°C) and lower (31.9 (0.1)°C) T_{suit} levels (see results). These probabilities can easily be calculated using the transformation $e^x/(1+e^x)$, where x represents the regressor part of the best-fitting regression model.

RESULTS

Induced temperatures

With the thermosuit approach, we were able to differentially manipulate proximal and distal skin temperature (see example of one night in one patient in fig 1). The temperature manipulations of the proximal part of the thermosuit accounted for 53.8% of the variance in mean $T_{skin\text{-}prox}$. $T_{skin\text{-}prox}$ averaged 35.1 (0.1)°C (mean (SEM) at the warmest level versus 34.7 (0.1)°C at the coolest level. Likewise, the independently manipulated temperature of the distal part of the thermosuit accounted for 44.0% of the variance in mean $T_{skin\text{-}dist}$. $T_{skin\text{-}dist}$ averaged 35.5 (0.05)°C at the warmest level versus 35.1 (0.05)°C at the coolest level. Thus, the manipulations forced the skin temperature to cycle slowly within a very subtle 0.4°C range (see temperature graph in fig 1). The manipulations left core body temperature virtually unchanged (skin temperature manipulations accounted for only 2.5% of the variance in core body temperature).

Effect of temperature manipulation on sleep stage distribution

Thermosuit manipulation of the temperature of the proximal and distal skin significantly affected sleep depth and the occurrence of wakefulness. Table 1 shows that proximal warming suppressed wakefulness (OR 0.81, CI (0.77 to 0.84), $p<0.001$) and enhanced slow-wave sleep (OR 1.23 (1.17 to 1.29), $p<0.001$; all OR expressed per 1°C increase in T_{suit}). In contrast, distal warming enhanced wakefulness (OR 1.11 (1.06 to 1.16), $p<0.001$) and stage 1 sleep (OR 1.22 (1.16 to 1.28), $p<0.001$) sleep at the cost of slow-wave sleep (OR 0.85 (0.81 to 0.89), $p<0.001$) and REM sleep (OR 0.87 (0.83 to 0.92), $p<0.001$). There were no significant effects on the occurrence of stage 2 sleep.

A graphical representation of the sleep-stage distribution is given in fig 2. As compared with the least favourable skin temperature combination, the optimal combination led to a 160% increase in slow-wave sleep, a 50% increase in REM sleep and a 68% decrease in wakefulness.

DISCUSSION

This study shows that subtle manipulation of proximal and distal skin temperatures has beneficial effects on nocturnal sleep in narcolepsy. When the proximal skin was warmed, slow-wave sleep increased, and wakefulness was suppressed. In contrast, warming of the distal skin suppressed slow-wave and REM sleep, while enhancing wakefulness and stage 1 sleep.

Fragmented nocturnal sleep is a major and difficult to treat problem for many patients with narcolepsy. Currently, treatment of this invalidating symptom is based on hypnotics, most notably sodium oxybate,[5] which increases slow-wave and REM sleep, while suppressing wakefulness.[3 22]

The present study was designed in such a way that different manipulation schemes were equally and randomly distributed over the test subjects in a balanced way. As such, the effects cannot have been caused by time of night or circadian effects, but can be solely attributed to the manipulation of skin temperature. The fact that subtle changes in skin temperature affect sleep in both narcoleptic patients and healthy controls[14] shows that the basic hypothalamic circuitry involved in temperature and sleep regulation is still responsive to manipulation in narcolepsy despite the hypocretin deficiency. In this study, no subject experienced the optimal or least beneficial combination of proximal and distal manipulations continuously during a full night. Furthermore, sleep time was restricted from midnight to 06:00. It would now be of interest to confirm the positive effects found in this study using a controlled trial in which the optimal or least beneficial temperature conditions are applied continuously throughout a full night.

In conclusion, despite the hypocretin deficiency, the basic hypothalamic circuitry involved in temperature and sleep regulation is still responsive to manipulations in narcolepsy. These results raise the intriguing possibility that selective manipulation of skin temperature within the comfortable range might in theory be applied to ameliorate one of the core symptoms of narcolepsy; disturbed nocturnal sleep.

Acknowledgements: This work was supported by grants from The Netherlands Organization for Scientific Research (projects SOW 014-90-001 and Innovation Grant 016.025.041) and the EU FP6 Sensation Integrated Project (FP6-507231). SO was supported by a VENI grant from The Netherlands Organization for Scientific Research (#916.56.103). We would like to thank J Stam (Academic Medical Center, Amsterdam) for clinical surveillance during the protocol. Furthermore, we are very grateful to S Wehrens, M Fisher, J Vis (NIN) and P van Someren (LUMC) for their invaluable help during the collection and analysis of the EEG data.

Competing interests: None.

Ethics approval: Ethics approval was provided by the Medical Ethics Committees of the Academic Medical Center in Amsterdam and the Leiden University Medical Center.

Patient consent: Obtained.

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Neurological picture

Massive fatal cerebral air embolism as a negative contrast angiogram

Cerebral gas embolism is a rare and potentially fatal event that may occur as a complication of medical procedures and trauma. Radiologic diagnosis is remarkable and favours immediate treatment. We present an unusual case of massive fatal cerebral air embolism, diagnosed with multidetector-row computed tomography (MDCT), where final appearance resembled a negative contrast angiogram.

CASE REPORT

A female patient born with a meningomyelocele developed chronic renal insufficiency. She underwent kidney transplantation from a cadaver donor when she was 20 years old.

The patient presented with persistent haematuria and haemoptysis 6 months after the procedure. A chest CT scan demonstrated multiple lung nodules with an intense enhancement pattern similar to aneurysms/pseudoaneurysms (fig 1A). Therefore, she underwent resection of the kidney transplant, with the histopathological finding of invasive urothelial carcinoma. Biopsy of the lung nodules also revealed vascular-invasive urothelial metastatic tumour.

Two days after discharge from the hospital, she suddenly presented with intense headache followed by loss of consciousness. Endotracheal intubation was performed in an emergency room near her house. She was then transferred to our facility.

A large cerebral haematoma in the right frontal lobe and intraventricular haemorrhage were shown on MDCT. Non-contrast images demonstrated multiple tubular air densities within the intracranial and extracranial circulations (fig 1B, C). Reconstructions using the minimum intensity projection technique undoubtedly demonstrated the intracranial gas embolism, delineating the circle of Willis in detail as a negative contrast angiogram (fig 1D).

Twenty-five minutes after MDCT was performed, the patient suffered irreversible cardiopulmonary arrest. An autopsy was refused.

DISCUSSION

Gas may get into the peripheral venous circulation, the right heart and then the left heart (paradoxical embolism) as one of the following mechanisms: open foramen ovale,[1] cardiac or pulmonary shunts.

The other possibility is the direct introduction of gas into the pulmonary veins, by means of barotrauma or procedures that may cause pleurovascular,[2] bronchovascular[3] or oesophagovascular fistulas.[1] There have been cases described following pulmonary biopsy,[3 4] use of venous catheters,[5] angiography[6] and even related to contrast injection.[7] It may also happen secondary to traumatic events and in scuba-diving incidents.[8]

We believe that positive pressure ventilation, in the presence of pulmonary vascular-invasive metastases, may have been responsible for the passage of gas from the bronchial tree directly into the pulmonary veins. The acute neurological symptoms presented by the patient were probably related to the cerebral haemorrhage, possibly associated with previously asymptomatic brain metastases.

Diagnosis is easily achieved with CT,[9] but may also be made using MRI.[8] Treatment includes haemodynamic support and hyperbaric oxygen therapy.[1 4] This entity carries a mortality rate of up to 23%.[7 10]

The vast majority of cases of cerebral air embolism exhibit only a minimal amount of gas in the intracranial circulation, and documentation of massive cases before death is exceedingly rare. The presenting case is illustrative of fatal cerebral air embolism, with the presence of gas delineating the intracranial circulation as a negative contrast angiogram.

C S Andrade, L T Lucato, C da Costa Leite

Department of Radiology of the Clinics Hospital of the University of Sao Paulo, School of Medicine, Sao Paulo, Brazil

Correspondence to: Celi Santos Andrade, Rua Capote Valente, 500, ap. 2216, Sao Paulo, S.P., Brazil, CEP 05409-000; celis.andrade@ig.com.br

Funding: None.

Competing interests: None.

J Neurol Neurosurg Psychiatry 2008;**79**:1357–1358. doi:10.1136/jnnp.2008.145938

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J Neurol Neurosurg Psychiatry 2008 79: 1354-1357 originally published online July 24, 2008
doi: 10.1136/jnnp.2008.143610