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RAPID COMMUNICATIONS
Clinical trials

Auditory stimulation of sleep slow waves enhances left ventricular function in humans

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Introduction

Although the impact of sleep on cardiovascular health is widely accepted,[1] precise mechanisms by which specific brain oscillations during sleep facilitate post-sleep cardiac function remain unclear. Slow waves, the prominent brain oscillations of non-rapid eye movement (NREM, here NREM Stage 2 + 3) sleep, are hypothesized to play a critical role in mediating the beneficial effects of sleep on cardiovascular functioning. Here, we used auditory stimulation to experimentally enhance slow waves and test whether that affects cardiovascular function during and after sleep.

Methods

Participants

Twenty-six healthy male participants were enrolled in this randomized controlled, double-blind, cross-over trial (ClinicalTrials.gov NCT04166916). Eight participants were excluded because they either did not meet predefined inclusion criteria during the screening night ($n = 7$) or because of failure to adhere to the experimental protocol ($n = 1$). The final population included 18 participants (age range: 30.0–57.1 years) who were non-smokers and had no cardiovascular or sleep disorder/comorbidity or significant concomitant diseases. The study was approved by the Cantonal Ethics Committee Zurich. All participants provided written informed consent before participation and received monetary compensation for their participation. The study was conducted in accordance with the Declaration of Helsinki.

Experimental procedure

An overview of the study is shown in *Figure 1A*. All applied measurement methods are described in more detail elsewhere.[2]

Three nights before each experimental night, participants followed a regular sleep/wake schedule, and on the day of the experimental night, participants abstained from naps, alcohol, intensive sports, caffeine, and any food 5 h before arriving at the sleep lab. After participants arrived, a venous blood sample was drawn before eating a standardized dinner, while a high-density electroencephalography system and two electrocardiography (ECG) electrodes were attached. Thereafter, we attached and calibrated the state-of-the-art non-invasive continuous blood pressure (BP) monitoring system Finapres Novascope. The sleep time (10–11 p.m.) was consistent for all experimental nights and chosen closest to the individuals' habitual bedtime. Participants could sleep for 7.5 h, while polysomnography, ECG,

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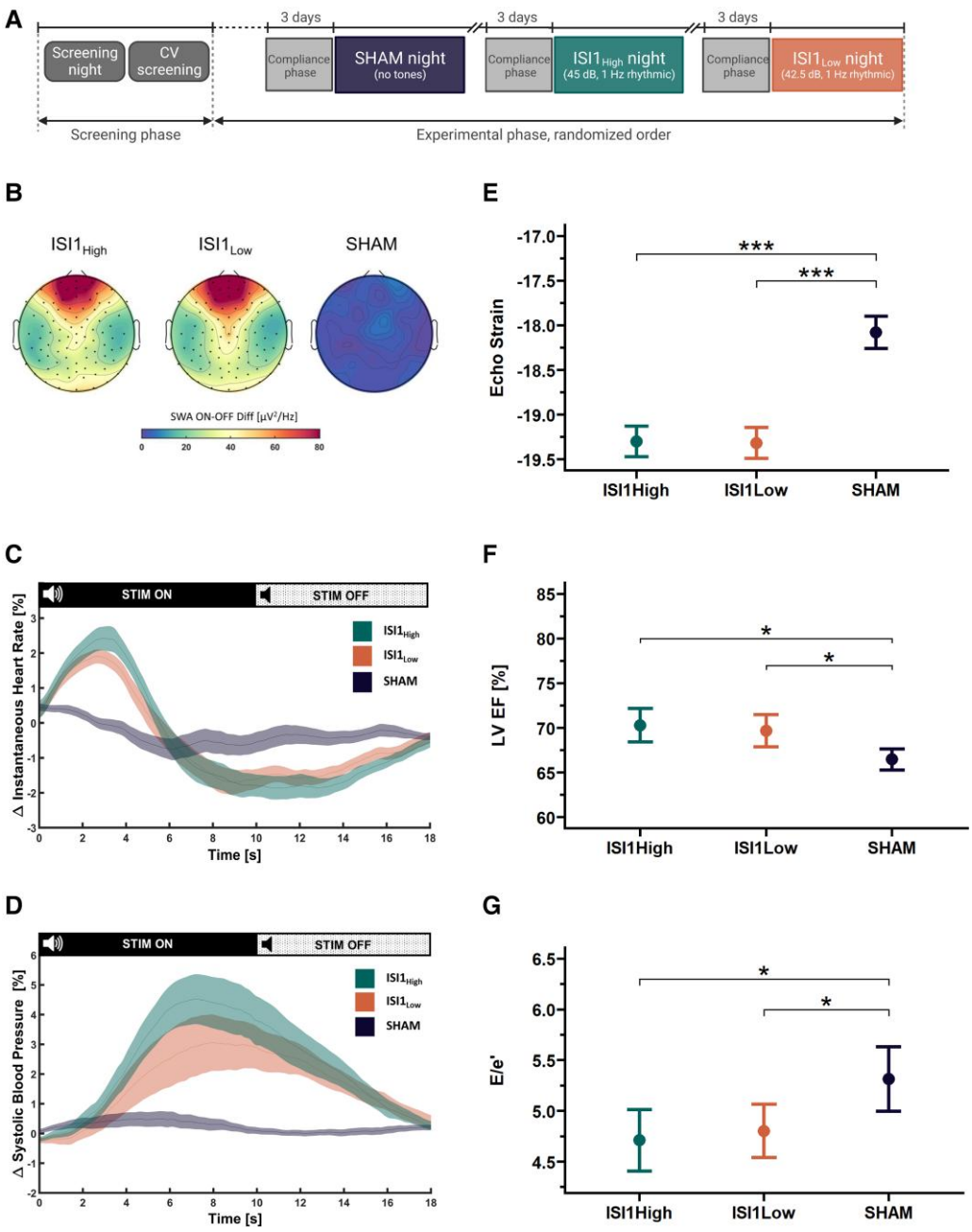

Figure 1 (*A*) Study protocol of clinical trial: the study started with a screening phase where the eligibility of participants was checked by an initial phone screening followed by a screening night in the sleep laboratory. If all inclusion/exclusion criteria were fulfilled, participants were invited to a cardiovascular screening to verify the absence of any cardiovascular disease. Afterwards, the experimental phase including three experimental nights took place. Three days prior to each experimental night, a compliance phase started where participants had to adhere to a regular sleep/wake schedule. The intervention conditions were administered in a pseudo-randomized order. (*B*) Topographical distribution of low slow wave activity (0.5–2.0 Hz) ON–OFF difference within the stimulation windows of the nights of the conditions $ISI1_{High}$, $ISI1_{Low}$, and SHAM. Highlighted dots indicate significant electrodes ($P < .05$) for the *post hoc P*-values applying linear-mixed effects models with condition entered as fixed factor and subject as random factor compared with the SHAM condition. *P*-values for each topoplot have been corrected for multiple comparisons by applying the false discovery rate. (*C*) Time course of relative instantaneous heart rate during the stimulation window for the conditions $ISI1_{High}$, $ISI1_{Low}$, and SHAM. Relative instantaneous heart rate change was calculated based on a two-beat heart rate baseline prior to the stimulation window. (*D*) Time course of the relative change of systolic blood pressure during the stimulation window. Relative blood pressure change was calculated based on a two-beat baseline prior to the stimulation window. (*E–G*) Post-sleep echocardiographic parameters presented as mean ± standard error of the mean. *P*-values have been computed based on a linear mixed-effect model with the fixed factor condition and random factor subject and were corrected for multiple comparisons by applying the Hochberg method. (*E*) Echo-strain: global longitudinal strain. $F(2,34) = 81.169$, $P < .001$. (*F*) LV EF: Left ventricular ejection fraction. $F(2,34) = 4.547$, $P = .018$. (*G*) *E*/*e'*: left ventricular filling pressure. $F(2,34) = 3.382$, $P = .046$. All data are shown for 18 participants. ***$P < .001$, **$P < .01$, *$P < .05$.

and BP were continuously recorded. Directly after waking up, another venous blood sample was drawn, followed by a standardized breakfast. Finally, the participants underwent an echocardiography recording. Other outcomes were assessed but not reported here.

Auditory sleep slow wave stimulation

Auditory stimulation of 50 ms bursts of pink noise each 1 s apart (1 Hz rhythmicity, interstimulus interval 1 [ISI1])[2] with a sound level of 45 dB ($ISI1_{High}$) or 42.5 dB ($ISI1_{Low}$) to achieve dose dependency was compared with a SHAM condition (no stimulation). Stimulations were delivered in a windowed 10 s ON (auditory stimulation presented) followed by 10 s OFF (no auditory stimulation presented) design (see[2,3] for a detailed description of stimulation algorithms) for a total of 4 h. Electroencephalography data of one SHAM night were excluded (technical failure).

Electroencephalography and cardiovascular parameters during sleep period

Sleep was scored visually for sleep stages according to 2007 American Academy of Sleep Medicine (AASM) criteria[4] and its respective update in 2012[5] but using 20 s epoch size as done previously.[2,3] We calculated low slow wave activity (0.5–2.0 Hz) ON–OFF difference as a measure of stimulation success.[3,6,7] Automatically detected and visually corrected ECG *R*-waves were extracted, and poor data quality segments of non-detectable *R*-waves were excluded. Segments of bad quality/artefacts of nocturnal diastolic and systolic BP were removed based on heart rate (HR) outliers of the BP device. Relative instantaneous HR (IHR) and BP during the stimulation window were calculated as a percentage difference to a two-beat baseline immediately preceding the start of each stimulation window. Only stimulation windows in artefact- and arousal-free NREM Stage 2 + 3 were included in further analyses.

Overnight and post-sleep cardiovascular parameters

Transthoracic echocardiography was performed by an experienced cardiologist, and the left ventricular ejection fraction (LVEF), left ventricular global longitudinal strain, and left ventricular *E*/*e*′ ratio (tissue Doppler imaging) were determined.

As an index for arterial stiffness, pulse wave velocity (PWV)[8] was assessed, each evening and the following morning according to the Association for Research into Arterial Structure and Physiology guidelines.[9] Seven measurements were missing because of problems in finding a valid signal. Additionally, we measured blood biomarkers related to inflammation (interleukin-6, interluekin-1β, and E-selectin) and triglycerides, HDL-cholesterol, and LDL-cholesterol. One subject was removed from the analysis because of multiple unsuccessful blood drawings.

Statistics

We compared the outcome variables using linear mixed-effects models (fixed factor: condition, random factor: subject). Overnight differences were calculated as morning–evening values. If the linear mixed-effects model was significant for condition, we derived *post hoc* *P*-values for $ISI1_{High}$ and $ISI1_{Low}$ each compared with SHAM corrected for multiple comparisons for each model separately using the Hochberg method. Visual inspection of the residual plots of the linear models did not reveal any obvious deviations from normality or homoscedasticity. *P*-values <.05 were considered statistically significant.

Results

Both auditory sleep stimulation conditions significantly and globally enhanced slow waves during times of stimulation (*Figure 1B*). Moreover, auditory stimulation influenced immediate cardiovascular dynamics as shown by a biphasic IHR response during the application of auditory stimulation (*Figure 1C*). The analysis of absolute systolic BP revealed no significant difference between conditions [$F(2,33.341) = 0.009$, $P = .991$]. However, after baseline correction, we found a small but consistent increase in relative systolic BP (*Figure 1D*).

We found a significant increase in left ventricular global longitudinal strain [$F(2,34) = 81.169$, $P < .001$], a significant increase in LVEF [$F(2,34) = 4.547$, $P = .018$], and a significant decrease in left ventricular *E*/*e*′ ratio [$F(2,34) = 3.382$, $P = .046$], all indicating improved left ventricular systolic and diastolic functions (*Figure 1E–G*) for both auditory stimulation conditions. Finally, overnight differences in blood biomarkers (all $P > .05$) and carotid-femoral PWV [$F(2,44) = 0.176$, $P = .839$] revealed no significant effect of the stimulation condition.

Discussion

Our results provide first evidence highlighting the role of sleep slow waves in enhancing left ventricular cardiac function. The replication of the cardiac effects after two independent stimulation nights underscores their robust nature and indicates the therapeutic potential of slow wave stimulation. However, the observed cardiovascular response during sleep might correspond to elevated sympathetic tone, which in sustained form could potentially be deleterious in patients. Therefore, understanding and addressing this aspect in future studies is crucial in ensuring its positive effect. Altogether, we hypothesize that the beneficial effects are primarily attributed to enhancing strongly synchronized slow waves (such as K-complexes), which modulate cardiovascular activity through autonomic activity during sleep and thereby contribute to cardiovascular homeostasis.[10]

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Declarations

Disclosure of Interest

C.L. is a member of the Scientific Advisory Board of Emma Sleep GmbH, which is not related to this work. R.H. is a founder and shareholder of Tosoo AG.

Data Availability

Source data required to reproduce the main figures and main conclusions of the manuscript is openly available here: https://doi.org/10.3929/ethz-b-000630802.

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Ethical Approval

This study was approved by the Cantonal Ethics Committee Zurich (reference number: KEK ZH, BASEC 2019-01538).

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is NCT04166916.

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