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Brief Communication

Acoustic stimulation time-locked to the beginning of sleep apnea events reduces oxygen desaturations: a pilot-study

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ABSTRACT

Study objectives: We aimed to determine whether bone-conducted acoustic stimulation could prematurely terminate sleep apnea events, thereby decreasing amplitude and duration of subsequent oxygen desaturation. As oxygen desaturation has been linked to cardiovascular consequences, we postulate this could be a viable therapy in some cases.

Methods: Eight patients with severe Obstructive Sleep Apnea (2 women, 45 [20–68] y.o. Apnea-Hypopnea Index: 77.7 ± 22.3/h) underwent polysomnography at the Lausanne University Sleep Center. Short acoustic stimulations were administered by bone conduction every second event of sleep apnea. Sounds were remotely administered using a Dreem® headband worn by patients while undergoing nocturnal polysomnography. Amplitude (%) and duration(s) of oxygen desaturations following terminated apneas were compared to that of non-stimulated previous and subsequent events.

Results: 549 stimulations (68.6 ± 38 sounds per patient) in N1 (16.2%), N2 (69.9%), N3 (4.2%), and REM(9.6%) were conducted. Compared to the previous and subsequent non-stimulated apnea, stimulations reduced event duration by 21.4% (-3.4 ± 7.2 s, $p < 0.0001$) while oxygen desaturation amplitude and duration were reduced by 30.4% (mean absolute difference ± SD: −1.9 ± 2.8%, $p < 0.0001$), and 39.6% (-5.7 ± 9.2 s, $p < 0.0001$) respectively. For these variables, each patient showed a significant improvement following acoustic stimulation. Sound-associated discomfort was rated 1.14 ± 1.53 on an 8 points scale (8 = worst) and only 6.8% of emitted sounds were perceived by the patients, suggesting a well-tolerated intervention.

Conclusions: Bone-conducted sound stimuli decreased apnea events duration as well as duration and amplitude of associated oxygen desaturations. Stimulations were well tolerated and rarely perceived by patients. This therapeutic approach deserves further investigation, with monitoring of effects on sleep quality, daytime function/sleepiness and cardiovascular parameters.

1. Introduction

Obstructive Sleep Apnea (OSA) is a frequent condition inducing repetitive arousals from sleep and oxygen desaturations, which has been shown to be associated with daytime sleepiness, long-term risk of hypertension, stroke, heart failure, diabetes, metabolic syndrome and depression [1–9].

Although arousals from sleep apnea induce sleepiness and transient nocturnal hypertension [10,11], oxygen desaturations in sleep apnea are the most consistent predictor of increased cardiovascular risk [12,13] suggesting that OSA treatments should aim primarily at reducing occurrence and amplitude of sleep apnea-associated oxygen desaturations. Since sleep apneas usually end with an arousal from sleep that allows breathing to resume, triggering an earlier awakening could decrease oxygen desaturations' severity by reducing apneas' duration.

The aim of this research was to determine if early termination of OSA could be generated by an arousal generated by bone-conducted sound-stimulation, thus decreasing the amplitude and duration of oxygen desaturation.

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2. Methods

2.1. Participants

As proof of concept, we recruited 8 OSA patients from the Center for Investigation and Research in Sleep (CIRS) in Lausanne University Hospital. Patients gave written consent and the study was approved by the Institutional Review Board. Inclusion criteria were: >18 years, ability to give informed consent, apnea/hypopnea index >30/h, obstructive apnea index >15/h, mean amplitude of desaturation (during diagnostic night) ≥5%. Exclusion criteria were: perception deafness, professional drivers or an inability to follow procedures.

2.2. Study design

This is a single-arm, open-label, monocentric proof-of-concept trial designed to assess the effect of sound stimulations sent every second apnea event so that stimulated and non-stimulated events could be compared at the same time during the night.

2.3. Study intervention

The intervention took place at the CIRS during overnight polysomnography (PSG) using an Embla N7000 system (Natus, Pleasanton, CA, USA). PSG sensors were setup in accordance with American Academy of Sleep Medicine (AASM) 2007 recommendations [14]. A nasal pressure sensor was used to record sleep disordered breathing. Sleep stages and arousals were scored according to the 2007 AASM manual using Remlogic software (Embla® Flaga, Reykjavik, Iceland), while respiratory events were scored according to the 2012 AASM criteria [15].

In addition, a Dreem©-headband (Dreem, Paris, France), remote controlled and customized for our trial, was worn throughout the night. This allowed bone-conducted sounds of different intensities to be emitted by the investigators. Patients' perceptual threshold was assessed while awake, in order to determine which sound intensity to start with during the night.

Every second apnea event was stimulated as soon as two missed breaths were detected on the polysomnography (approximatively 6 s of nasal flow cessation). Sound stimulation was initiated using a 1000 Hz sound lasting 500 ms. Intensity was set at 10% above subject's own perceptual threshold. As stimulation proceeded, sound was adjusted continuously according to response to the previous stimulation as detailed below:

- If no breathing was observed after a sound stimulation during an event, volume was increased by 5%. If the maximum intensity was already reached, sound duration was increased from 500 ms to 1000 ms or 2000 ms.
- If the sound at a given intensity was able to terminate respiratory events without a full arousal, sounds parameters were unchanged.
- When a full cortical (EEG) awakening (AASM 2007 definition [14]) was observed as a result of the previous stimulation, intensity was decreased by 5%.

Upon awakening, patients were asked to answer the following two questions:

1. How many sounds did you hear throughout the night?
2. How tolerable was the stimuli (0–8 from not annoying to extremely unpleasant)?

2.4. Statistical analysis

All statistical analyses were performed using SPSS Statistics (IBM, Armonk, USA) or Prism 8 (GraphPad, San Diego, USA). The primary endpoint was the amplitude and duration of blood oxygen desaturations. Differences (% SaO_2) between baseline (before the apnea) and at nadir saturation reached during the event were calculated. Other endpoints were events' duration(s), desaturations' duration (s) and desaturations' nadir reached after an event (%). For each of these endpoints, a two-tailed paired Student's T-test was used to assess differences between stimulated and unstimulated respiratory events. For each stimulated event, the mean of the previous and the next respiratory event's parameters was used as the reference.

3. Results

Eight patients with severe OSA (6 men, mean age 45 y.o [20–68], mean Apnea-Hypopnea Index (AHI): 77.7 ± 22.3/h, mean Obstructive Apnea Index: 45.8 ± 17.1/h), mean BMI of 36.2 ± 7.2 kg/m^2, and a mean waist-hip circumference ratio (N = 7) of 0.97 ± 0.1 were studied.

Fig. 1 shows an example of sound stimulation and its effect on desaturation following the respiratory event. In total, 549 respiratory events were stimulated with 302 sounds of 500 ms, 217 of 1000 ms and 30 of more than 1000 ms with a total of 222 sounds at maximum volume.

Analysis of 549 paired respiratory events (stimulated and control) across the 8 participants showed a 30.4% reduction (mean absolute difference±SD: −1.9 ± 2.8%, $p < 0.0001$) in oxygen desaturation amplitude in stimulated events compared to the mean of previous and subsequent non-stimulated respiratory events. Fig. 2 shows the mean amplitude of oxygen desaturation in stimulated vs non stimulated respiratory events for each patient.

Overall, we observed a relative reduction of 38 ± 18% in oxygen desaturation amplitude. Moreover, desaturations' duration decreased by 39.6% (-5.7 ± 9.2s, $p < 0.0001$), the apneas' duration by 21.4% (3.4 ± 7.2s, $p < 0.0001$) and the absolute nadir oxygen saturation increased by 1.66% ± 5.69% ($p < 0.0001$) with the sound stimulations.

Sound stimulations had positive effects on oxygen desaturation amplitude regardless of sleep stage. In N1, 89 (16.2%) respiratory events were stimulated, in N2: 384 (69.9%), in N3: 23 (4.2%) and in REM sleep: 53 (9.6%). There was a significant difference between stimulated and control events for each sleep stage (N1;-2.34 ± 2.10, p-value < 0.0001), (N2; −1.75 ± 2.78, p=<0.0001), (N3; −1.07 ± 1.9, p = 0.0133) and (REM; −2.42 ± 4.06, p=<0.0001).

As assessed by the questionnaire given in the morning, sound-associated discomfort was rated 1.14 ± 1.53 on an 8 points scale where 8 was described as terribly uncomfortable and 0 as completely indifferent. Moreover, out of the 68 ± 38.3 sound stimulations applied per patient on average, only 5.36 ± 4.9 were perceived.

4. Discussion

This proof-of-concept study suggests that bone-conducted sound stimulations can significantly reduce apnea duration and amplitude/duration of apnea-induced oxygen desaturations in severe OSA patients, independent of sleep stage and without any subjective report of major discomfort. Our hypothesis is that this effect is probably due to sound-induced microarousals that reactivate brain stem breathing centers, which stimulate upper airway dilator muscles allowing upper airway to reopen and breathing to resume.

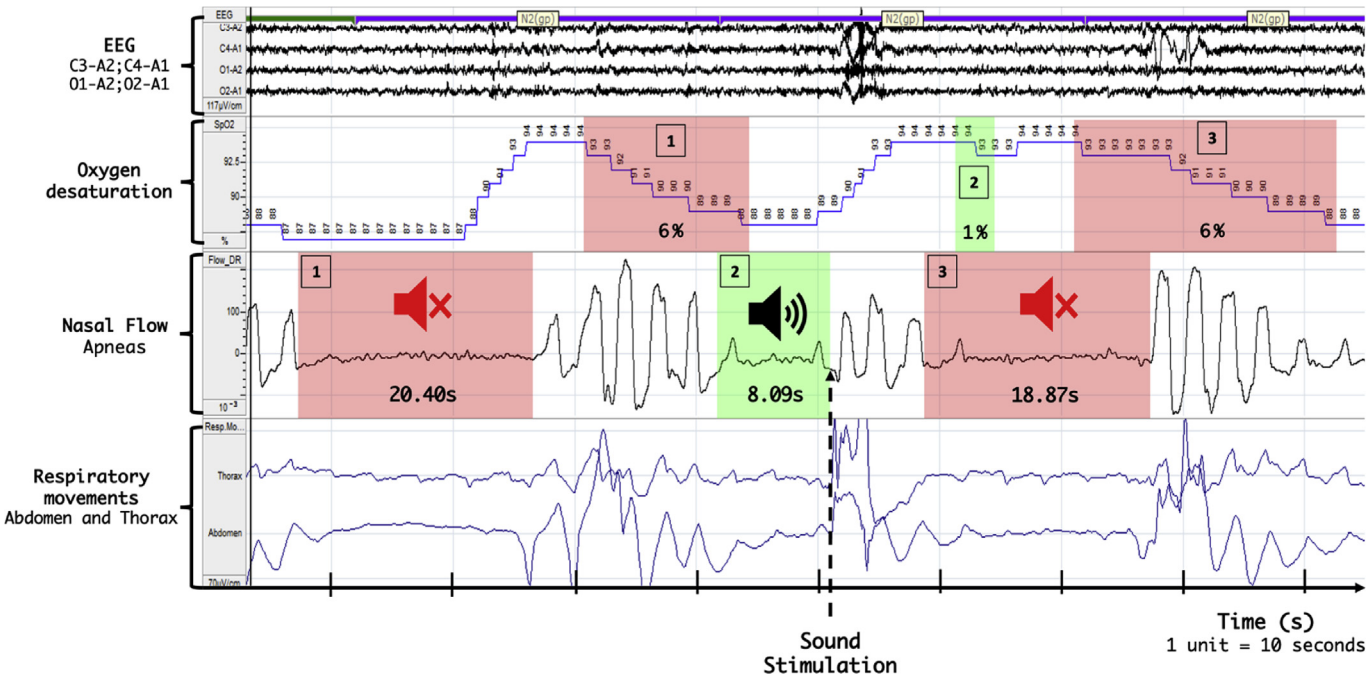
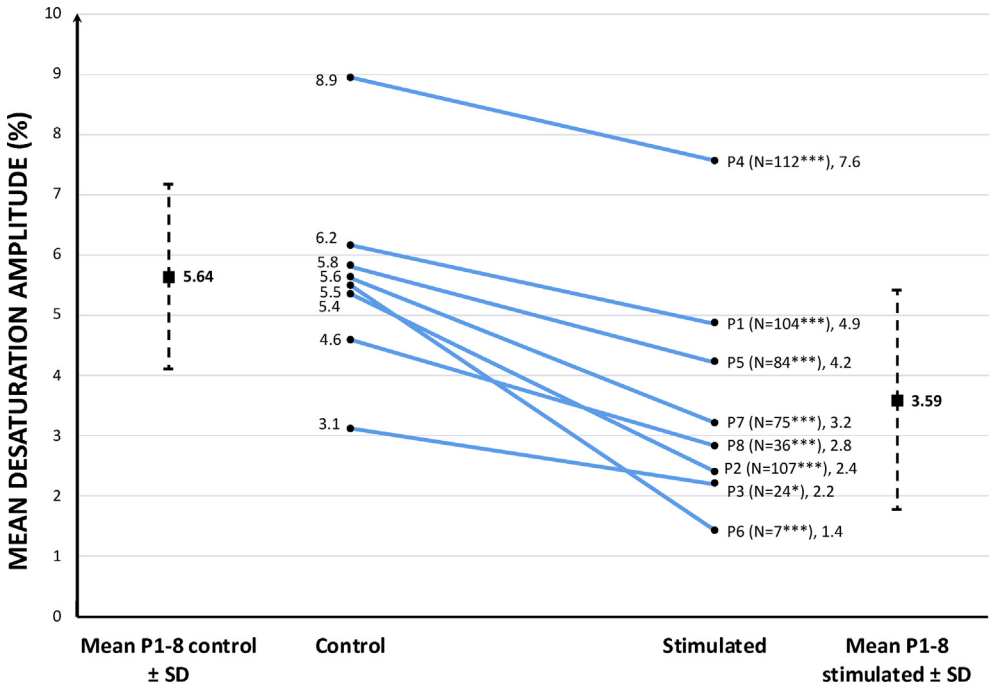


Fig. 1. Representative illustration of 3 polysomnography epochs with 1 stimulated and 2 control (unstimulated) apnea events. *EEG= electroencephalogram. Red box = unstimulated (control) respiratory event. Green box = stimulated event*. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)



Participant (Number of event)	Events	Mean O2 desaturation (%)	Std. Deviation	Effect of stimulation (%)	P-value paired t-test
All events (N=549)	Stimulated	4.32	3.31	-30.4	<0.0001
	Control	6.20	2.49		
Mean of P1-8	Stimulated	3.59	1.82	-38±18%	0.0008
	Control	5.64	1.53		

Fig. 2. Effect of sound stimulation on mean oxygen desaturation. Stimulated and non-stimulated events were compared between the 8 participants (Px = Participant x), P-value<0.5*; **P-value<0.01; ***P-value<0.001.

The method used in this trial might seem counterintuitive as we are aiming to mitigate a sleep disorder by inducing arousals from sleep. However, as apneas usually end anyway with an arousal, this method probably does not increase arousal number but decreases the associated hypoxic burden, an effect which may in turn reduce OSA associated cardiovascular risk [12]. Although oxygen desaturation seems to be the main pathophysiological factor responsible for OSA-associated negative outcomes, the proposed technique would obviously not reduce OSA-associated sleep fragmentation and will likely have no positive impact on daytime sleepiness.

The present pilot study has significant limitations. The sample included only 2 women (6 men) and all had severe OSA. However, this approach could probably also be applied to patients with milder sleep apnea since the acoustic-induced response of the breathing centers is probably independent of OSA severity. Although our results suggest that this technique decreases OSA severity, desaturations could not be completely prevented, and sound stimulations' impact on clinical parameters (sleep structure, daytime sleepiness, blood pressure etc..) was not assessed. We also specifically selected patients with frequent "trains of apnea" with complete breathing cessation, since the duration of apnea events is easier to assess (less "observer dependant"). This concept also needs to be further studied in a larger and more diverse group of patients suffering from different OSA severity levels (including hypopnea and apneas). Additionally, better measures of daytime functioning will need to be studied to ensure limited effects on daytime cognition and sleepiness.

In spite of these limitations, the technique has significant potential. For example, it could easily be optimized to yield better results through automatic detection of breathing variations using machine learning algorithms on snoring sounds or nasal pressure changes, allowing stimulation to be more efficient at reducing desaturations amplitude and duration. A real-time adaptation of sound intensity by intelligent algorithms according to responses to prior stimuli and sleep stage could allow generation of subcortical arousals instead of full EEG arousals, which may be sufficient to end the respiratory events with a lesser impact on sleep structure.

Another group previously investigated the concept of shortening respiratory events, with a different technique using a kinesthetic stimulation at the mastoid level with some positive results [16]. One could wonder whether a combination of mild bone conducted sound and kinesthetic stimulation could show a synergistic effect and allow a greater decrease in desaturations' amplitude.

5. Conclusion

This proof-of-concept clinical trial suggests that sound stimulation can significantly reduce amplitude and duration of desaturations in sleep apnea. This approach should however be further investigated, with monitoring of its effect on sleep quality, daytime sleepiness and cardiovascular parameters. Several avenues of improvement of this technique using engineering sciences are emerging and could increase its positive impact on OSA.

Clinical trial

Details:

Brief Title: Early Sleep Apnea Termination Using Sound Stimulation (ESAT).

Identifiers: NCT03753971.

Unique Protocol ID: 19121997 (clinicaltrial.gov).

Secondary IDs: 2018–02033 (swissethics.ch).

Ethics Committee: Commission cantonale d'Éthique de la Recherche sur l'être humain Vaud (CER-VD).

Statement of significance

Adherence to continuous positive airway pressure as a treatment for sleep apnea is poor, hence alternative treatments are needed. We attempted to prematurely terminate apneas using bone-conducted sound stimulation in order to reduce oxygen desaturation's amplitude. This proof of concept trial was a first step to assess the feasibility of this new treatment approach. The method can be improved in several aspects and further investigations are required to assess the impact of the sound stimulation on sleep quality, daytime sleepiness and cardiovascular parameters.

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CRediT authorship contribution statement

Adrien Waeber: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Visualization. **Pierrick J. Arnal:** Software, Writing - review & editing. **Gianpaolo Lecciso:** Data curation. **David Albir:** Data curation. **Emmanuel Mignot:** Writing - review & editing. **Raphael Heinzer:** Conceptualization, Methodology, Validation, Resources, Supervision.

Conflict of interest

Funded by the CIRS research fund. P. J. Arnal is employee of Dreem sas, Pr. R. Heinzer and Pr. E. Mignot are members of the scientific advisory board of Dreem. The Dreem® headbands used to generate the sounds have been given by Dreem.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.12.006.

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