## Mini-Symposia Title:

New developments in Sleep Bioengineering: 3. A deeper dive into new clinical findings in sleep-disordered breathing

**Mini-Symposia Organizer Name & Affiliation:**

Michael C.K. Khoo, PhD, University of Southern California, Los Angeles, USA,and Thomas Penzel, PhD, Charite University

**Mini-Symposia Speaker Name & Affiliation 1:**

Richard Jones, PhD, New Zealand Brain Research Institute and University of Canterbury, Christchurch, New Zealand

**Mini-Symposia Speaker Name & Affiliation 2:**

Ali Azarbarzin, PhD, Harvard Medical School and Brigham & Women's Hospital, Boston, MA, USA.

**Mini-Symposia Speaker Name & Affiliation 3:**

Patjanaporn Chalacheva, PhD, and Michael C.K. Khoo, PhD, Carnegie Mellon Univ., Pittsburgh, PA, and University of Southern

**Mini-Symposia Speaker Name & Affiliation 4:**

**S Mini-Symposia Speaker Name & Affiliation 5:**

**Mini-Symposia Speaker Name & Affiliation 6:**

## Theme:

- ○ 01. Biomedical Signal Processing
- ○ 02. Biomedical Imaging and Image Processing
- ○ 03. Micro/Nano-bioengineering; Cellular/Tissue Engineering &
- ○ 04. Computational Systems & Synthetic Biology; Multiscale modeling
- ◉ 05. Cardiovascular and Respiratory Systems Engineering
- ○ 06. Neural and Rehabilitation Engineering
- ○ 07. Biomedical Sensors and Wearable Systems
- ○ 08. Biorobotics and Biomechanics
- ○ 09. Therapeutic & Diagnostic Systems and Technologies
- ○ 10. Biomedical & Health Informatics
- ○ 11. Biomedical Engineering Education and Society
- ○ 12. Translational Engineering for Healthcare Innovation and Commercialization

**Mini-Symposia Synopsis— Max 2000 Characters**

Insufficient sleep has been identified as an epidemic of global proportions, with chronic insomnia and sleep apnea being the most prevalent forms of sleep disorders. Due to the close association between sleep regulation and the key physiological organ systems, disruption of sleep continuity can adversely affect cardiorespiratory and metabolic function, leading to associated morbidities such as cardiovascular disease and diabetes. The pathological changes in the cardiorespiratory and metabolic systems can subsequently "feed back" to impact sleep quality. The dynamic interactions between these systems give rise to the spontaneous variabilities evident in measurements of respiration, heart rate, blood pressure and sleep-wake state. Clever analysis of these signals, using novel algorithms and new technologies, can yield insight into the underlying mechanisms for the pathologies that result from these sleep disorders, and also lead to improved diagnostic and therapeutic approaches. In this series of 3 mini-symposia, an interdisciplinary panel of experts in the field will present state-of-the-art advances in our understanding of these complex phenomena and the quantitative tools that have been developed to better characterize them. This series of minisymposia follows in the tradition of similarly themed minisymposia series on sleep that we have organized for EMBC over the past several years, which have attracted considerable interest among EMBC attendees. The third minisymposium session will examine a variety of clinical issues related to the treatment and consequences of sleep apnea from a bioengineering perspective.

Synopsis of Talk #1

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# Cerebral perfusion, cognition, microsleeps, and drowsiness in people with moderate-OSA: Before and after six months of CPAP

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## I. Introduction

Obstructive sleep apnoea (OSA) is a common sleep disorder characterized by cyclical oxygen desaturation, sleep fragmentation, and, in turn, excessive daytime sleepiness and a substantially increased propensity for microsleeps and risk of fatal accidents on the road. There is substantial evidence to show that severe OSA (AHI ≥ 30) is associated with increased risk of hypertension, cardiovascular disease, stroke, cognitive dysfunction, and decreased cerebral perfusion when awake.

We have carried out a longitudinal study to investigate (i) Do patients with moderate OSA (AHI = 15–30) have reduced cerebral perfusion, reduced cognition, increased drowsiness, and/or increased microsleep propensity? and (ii) Can CPAP slow down, stop, or even reverse the decline of these functions in patients with moderate OSA?

## II. Methods

### A. Subjects

Participants were 24 patients who had been referred to a Sleep Unit and subsequently diagnosed with moderate OSA (AHI = 15–30) and 7 controls (AHI = 0–5).

### B. Tests

Cerebral perfusion and structural images were obtained using a 3-T MRI scanner. Arterial spin labeling perfusion imaging was used to quantify cerebral perfusion. Cognition was assessed on a range of visuoperceptual and central executive cognitive tests. Microsleep propensity was assessed from visuomotor performance and eye-video on a 30-min 2-D tracking task. Drowsiness was self-reported on the Epworth Sleepiness Scale (ESS) and estimated in the MRI scanner by the tester on the Wierwille & Ellsworth scoring method sleepiness scale.

### C. Procedure

The patients with moderate OSA were divided into two groups: 13 who received 6 months of CPAP treatment (*Autoset* 10, ResMed Ltd) and 11 who had no treatment. All patients were assessed via Level-2 sleep studies at baseline and at 6 months.

## III. Results

At baseline, there was no significant difference in cerebral perfusion (global or regional), cognitive functions, or microsleep propensity between the moderate OSA patients and the control subjects. There were also no significant within-subject changes in perfusion, cognitive functions, or microsleep propensity between baseline and 6 months in either the CPAP on non-CPAP moderate-OSA groups or the control group.

Conversely, ESS was higher at baseline in the combined moderate-OSA group ($p < .001$) and improved over the 6 months in the treated moderate-OSA group ($p = .004$).

Furthermore, 12 of the 13 CPAP-treated patients considered that they had benefitted from the CPAP treatment to the extent that they wished to continue on CPAP following the study.

## IV. Conclusion

Our study found no evidence to show that people with moderate OSA have impaired cerebral perfusion, impaired cognition, or increased microsleep propensity. Furthermore, there was no evidence to show that these measures got worse if untreated over a 6-month period. Thus, as opposed to severe OSA, moderate OSA appears to have, at most, a minimal adverse effect on brain function. Consequently, on this basis, there is no justification for initiating CPAP treatment in people with moderate OSA.

Conversely, while there is no evidence of moderate OSA causing (potentially irreversible) physiological or structural brain damage, there appears to be substantial potential benefit from CPAP by way of improvement of quality of sleep and, in turn, lessening of excessive daytime sleepiness. This benefit seems to be at a level which is more than sufficient to counter the less appealing aspects of CPAP treatment.

Synopsis of Talk #2

# Prognostic biomarkers of sleep apnea-related cardiovascular morbidity and mortality

**Ali Azarbarzin, PhD**

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## INTRODUCTION

The acute consequences of apneas and hypopneas (respiratory events) are intermittent hypoxia/hypercapnia, arousals, and intrathoracic pressure swings, all of which are thought to elicit an autonomic response. As a quantitative measure of OSA-related hypoxia, hypoxic burden (HB) was shown to predict cardiovascular (CV) mortality (Azarbarzin et al., Eur Heart J 40:1149-1157, 2019). In addition to the severity of intermittent hypoxia, we hypothesize that individuals with elevated autonomic responses (post-event tachycardia) are at higher risk for cardiovascular consequences of OSA. Here, we sought to examine the combined effect of HB and post-event tachycardia on CV morbidity and mortality.

## METHODS

In 4099 individuals from the Sleep Heart Health Study with at least 30 respiratory events (age: 64.2±11.5 years; 53.3% women), we quantified post-event tachycardia (ΔHR, (Azarbarzin et al., Sleep 36:881-889, 2013)) as the maximum increase in heart rate from a local baseline (event termination ±100 s); each individual was given a mean ΔHR response. HB was defined as the total area under event-related desaturation curves. By combining HB and ΔHR, we aimed to quantify the frequency of events and their desaturation severity, as well as their autonomic responses. The adjusted hazard ratios for incident CVD, CV mortality, and all-cause mortality were quantified using Cox Proportional Hazard models, after adjusting for many potential confounders and mediators.

## RESULTS

Over 10.7±3.2 years, there were 961 incident CVD events, 316 CV-related deaths, and 985 all-cause deaths. Individuals with high ΔHR and high HB had a significantly increased hazard ratio for incident CVD, CV-related mortality, and all-cause mortality, respectively.

## CONCLUSIONS

Individuals with OSA characterized by a high HB and a large autonomic response to OSA as evidenced by a high ΔHR are at increased risk of cardiovascular morbidity and mortality. This study identifies important prognostic biomarkers for OSA that may improve patient selection into CVD-intervention clinical trials.

Synopsis of Talk #3:

# Association of peripheral vasoconstriction during arousal from sleep-disordered breathing with vaso-occlusive pain in sickle cell disease

**Patjanaporn Chalacheva, PhD, and Michael C.K. Khoo, PhD**

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## INTRODUCTION

Sleep-related disorders, such as obstructive sleep apnea (OSA) and periodic limb movements (PLM), are common in children with sickle cell anemia (SCA). A previous multi-center prospective cohort study addressed the question of whether nocturnal oxygen desaturation arising from OSA might predict incidence of vaso-occlusive crisis in this population. However, no significant association was found between the incidence of severe pain episodes and low mean nocturnal SpO2 or severity of OSA. On the other hand, it is well-established that transient surges in sympathetic activity generally accompany respiratory-related and spontaneous arousals, as well as limb movements, in OSA and PLM. These sympathetic surges lead to peripheral vasoconstriction that reduce microvascular blood flow and increase the likelihood of triggering painful vaso-occlusive crises that are the hallmark of SCA. The primary goal of this study was to determine if there is a positive association between the strength and duration of peripheral vasoconstriction events during sleep and rate of incidence of severe pain episodes in SCA subjects.

## METHODS

The data analyzed were extracted from the polysomnograms (PSG) and clinical records of 212 children (4-18 years), who were participants in the multi-center prospective SCA cohort study reported by Willen et al. (Am J Hematology 2018; 93:478-485). Our analyses focused on the whole-night time-series of R-R intervals (RRI) derived from the electrocardiogram and beat-to-beat amplitudes (PPGa) of finger photoplethysmograph, along with summary information derived from the scored PSG.

The PPGa time-series in each PSG was first lowpass-filtered to remove fluctuations related to tidal breathing. Subsequently, vasoconstrictions that were classified as significant were detected by applying an algorithm in which negative deviations from running local baseline exceeded a threshold level of change. The changes in RRI from the pre-vasoconstriction RRI level were also computed. Compact descriptors of PPGa reduction, such as the duration, average magnitude (Mvasoc) and area under the curve, were extracted from each significant vasoconstriction. The median values of these compact descriptors were taken to represent the nocturnal vasoconstriction characteristics of each subject. The average rate of incidence of severe pain events from the PSG date to the end of follow-up for each subject was deduced from the Willen study. Due to the positively skewed distribution of the pain-rate data, negative binomial regression was used to relate pain-rate as the outcome variable to the predictor variables, which included: vasoconstriction descriptors, sleep disturbance indices (eg. arousal index and PLM index), age, sex, hemoglobin level and hydoxyurea (treatment) status.

## RESULTS

Pain-rate was found to be associated with Mvasoc ($p=0.032$), with larger Mvasoc predicting more pain, after accounting for age, hemoglobin level and hydroxyurea status. Mvasoc was strongly correlated with arousal index ($p=0.0056$) and the frequency of limb movements ($p=0.0124$). However, neither arousal index nor frequency of limb movements were good predictors of pain category. On the other hand, age was a consistent predictor of pain category, with higher age associated with high pain.

## DISCUSSION & CONCLUSIONS

Our working hypothesis is that reductions in regional blood flow increase the likelihood of entrapment of sickled red blood cells in the microvasculature by prolonging capillary transit time, thereby predisposing to vaso-occlusive crisis. During sleep, transient decreases in microvascular flow can occur during sympathetically-mediated events, such as arousals or limb movements, that precipitate peripheral vasoconstriction. Our finding of a significant association between the strength of peripheral vasoconstriction and the incidence of acute severe pain episodes in children with SCA supports this hypothesis. An interesting and somewhat unexpected finding was that the indices reflecting frequency or duration of sympathetic surges, such as arousal index, frequency of limb movements and vasoconstriction duration, were not predictive of pain category. Instead, the strength of the vascular response to these sympathetic surges was the only variable that displayed significant association with sickle-cell pain.