Mini-Symposia Title:

ADVANCES IN SLEEP BIOENGINEERING I: Markers for OSA screening and early detection of sleep-related adverse events

Mini-Symposia Organizer Name & Affiliation:

Michael C.K. Khoo, USC, Los Angeles; Thomas Penzel, Charite University Hospital, Berlin; Philip deChazal, UNSW, Sydney.

Mini-Symposia Speaker Name & Affiliation 1:

Ali Azarbarzin, Harvard Medical School, Boston

Mini-Symposia Speaker Name & Affiliation 2:

Nasim Montazeri and Azadeh Yadollahi, University of Toronto, Toronto.

Mini-Symposia Speaker Name & Affiliation 3:

Ahmed Metwally, Stanford University, Palo Alto.

Mini-Symposia Speaker Name & Affiliation 4:

Michael Khoo, USC, Los Angeles, and Patjanaporn Chalacheva, Carnegie Mellon University, Pittsburgh.

S Mini-Symposia Speaker Name & Affiliation 5:

Mini-Symposia Speaker Name & Affiliation 6:

- ◯ 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 or fragmented sleep has been identified as a public health epidemic. The most prevalent causes include chronic insomnia and obstructive sleep apnea (OSA), which affect almost a billion people. OSA is associated with increased risk of developing a rapidly expanding list of medical comorbidities such as hypertension, cardiac arrhythmias, ischemic heart disease, stroke, diabetes, learning and attention deficits, and depression and mental illness. While the underlying pathophysiology of various endotypes of OSA and their impact on other organ systems remain to be completely understood, the availability of low-cost "smart" technology, along with increasing computational power, are fueling novel advances in improved methods of nonintrusive diagnostics and therapeutic management of the syndrome. In this series of 3 minisymposia, established experts in the fields of cardiorespiratory and sleep research will present their latest findings in a broad spectrum of areas in sleep medicine. This first minisymposium session will focus on the use of nonintrusive measurements and wearable devices for early detection of OSA and its downstream consequences, as well as other sleep-related comorbidities. Brief speaker biographies: (1) Ali Azarbarzin, PhD, Instructor in Medicine, Division of Sleep and Circadian Disorders, Harvard Medical School; (2) Nasim Montazeri, PhD, Postdoctoral Fellow, and Azadeh Yadollahi, PhD, Asst Professor of Biomedical Engineering, University of Toronto; (3) Ahmed Metwally, PhD, Senior Bioinformatics/ AI Scientist, Illumina, Inc. and Postdoctoral Scholar, Stanford University; (4) Michael Khoo, PhD, Professor of Biomedical Engineering & Pediatrics, Univ. of Southern California, and Patjanaporn Chalacheva, PhD, Asst. Teaching Professor of Biomedical Engineering, Carnegie Mellon University, Pittsburgh.

Theme:

- ◯ 01. Biomedical Signal Processing
- ◯ 02. Biomedical Imaging and Image Processing

Lung to Finger Circulation Time as a Marker of Cardiovascular Mortality Among Older Men with Sleep Disordered Breathing

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[1]Division of Sleep and Circadian Disorders, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA; [2]Department of Medicine, University of Washington, Seattle, WA.

Abstract—**Conventional metrics to evaluate sleep disordered breathing (SDB) have many limitations including their inability to identify subclinical markers of cardiovascular dysfunction. In this study, the goal was to examine the clinical utility of Lung to Finger Circulation Time (LFCT) as a marker of mortality in older men with obstructive sleep apnea (OSA). The sample included 2631 older men enrolled in the multi-center Outcomes of Sleep Disorders in Older Men (MrOS Sleep) study. In the adjusted analysis, men in the 4th quartile of LFCT (22-52 s) had an increased risk for cardiovascular-related (36%[95% CI: 2-81%]) and all-cause mortality (35%[95% CI: 14-60%]), when compared to men in the 1st quartile (4-15 s). In conclusion, sleep study-derived LFCT is associated with both CV and all-cause mortality in older men, independent of baseline CV burden and SDB metrics. LFCT may be a novel physiologic marker for CV vulnerability and adverse outcomes in patients with SDB.**

I. INTRODUCTION

Sleep disordered breathing (SDB) is a common condition associated with cardiovascular disease (CVD) and mortality. Although conventional metrics focusing on the quantification of respiratory events are useful in the diagnosis of SDB, they may not accurately reflect the complex pathophysiological consequences of SDB on the cardiovascular system.

II. METHODS

We derived average lung to finger circulation time (LFCT) from sleep studies in community dwelling older men enrolled in the multi-center Outcomes of Sleep Disorders in Older Men (MrOS Sleep) study. LFCT was defined as the average time between end of scored respiratory events and nadir oxygen desaturations associated with those events. Adjusted hazards ratios for the cardiovascular and all-cause mortality by LFCT quartiles were quantified. In the multivariable Cox regression models, the hazard ratios were adjusted for demographic, body habitus, baseline CVD. Additional model included apnea-hypopnea index (AHI), hypoxic burden, and time with SpO_2 below 90%. We also repeated analyses after excluding those with CVD at baseline.

III. RESULTS

A total of 2631 men (mean age 76.4 ± 5.5 years) were included in this study. LFCT median [IQR] was 18 [15-22] s. During average follow up of 9.9 ± 3.5 years, 427 (16%) and 1205 (46%) men experienced cardiovascular-related and all-cause death, respectively. In multivariable analysis, men in the 4th quartile of LFCT (22-52 s) had a HR of 1.36 [95% CI =1.02, 1.81] and of 1.35 [1.14, 1.60] for CV and all-cause mortality, respectively, when compared to men in the 1st quartile (4-15 s). The results were similar when additionally adjusting for AHI, hypoxic burden, or time with SpO_2 below 90%. Results were stronger among men with no history of CVD at baseline.

IV. DISCUSSION & CONCLUSION

In conclusion, our prospective analysis showed that sleep study-derived Ct (LFCT) was independently associated with both cardiovascular-related and all-cause mortality in older men with SDB independent of baseline CVD and conventional SDB metrics. LFCT may be a novel physiologic marker for subclinical CVD and adverse outcomes in patients with SDB.

ACKNOWLEDGMENT

Tracheal Signals Analysis for Sleep Apnea Screening

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Sleep apnea is a chronic and age-related progressive condition. Sleep apnea is associated with repetitive pauses (apnea) or reductions (hypopnea) in the respiration during sleep, leading to impaired oxygenation, daytime sleepiness and increased risk of cardiovascular, metabolic, and mental disorders, and car/work collisions. The severity of sleep apnea is clinically reported by the average number of apneas and hypopneas per hour of sleep. To diagnose sleep apnea, the person with related symptoms such as snoring or daytime sleepiness undergoes an overnight in-laboratory polysomnography (PSG). PSG is expensive and requires individuals to wait between 2 to 60 months to take the test and tolerate the attachment of more than 20 sensors to their body during the test, which could compromise normal sleep and the presentation of sleep apnea. Therefore, up to 85% of individuals with high risk of sleep apnea are not diagnosed. To address these challenges, portable home-based devices with fewer sensors have been developed for screening sleep apnea and estimating AHI.

One of the modalities in portable sleep screening devices is through recording tracheal sounds and movements called as tracheal signals. The respiratory related movements over the chest create caudal vibrations over the trachea that can be extracted from tracheal movements. Furthermore, there is a well-established relationship between respiratory airflow and the energy of tracheal sounds. Due to the proximity of the trachea to the source of snoring in the upper airway, tracheal sound is a less noisy signal to analyze the characteristics of snoring. Therefore, tracheal signals are plausible modalities for estimating airflow signal and AHI for implementing a convenient sleep screening even at home settings.

We have developed a device, The Patch, that includes a microphone and an accelerometer to record tracheal signals. Through conducting an extensive study on individuals with suspected sleep apnea, we have developed algorithms to estimate airflow signal and AHI. Accurate estimation of airflow from tracheal signals requires identification of respiratory phases (accuracy of 83.7% for inspirations and 75.0% for expirations) and extracting an estimate of changes in the respiration intensity (tidal volume). In one of recent studies, we have shown that the estimated tidal volume can significantly decrease during apnea/hypopnea. Therefore, we further analyzed the estimated tidal volume to detect respiratory events. To estimate AHI from the detected number of events, sleeping time is required. We have shown that compared to wakefulness, respiration can change during sleep, and such changes affect tracheal signals. By detecting the sleeping periods from tracheal signals (accuracy of 82.3±8.66 %, R=0.78, p<0.001 with PSG), we have provided a more accurate estimate of AHI (R=0.82, p<0.001). Finally, along with the detected number of events, we incorporated snoring characteristics in a mathematical model to improved AHI estimation (R=0.87, p<0.001).

This was the first extensive study to use only tracheal signals for estimating airflow and sleep apnea severity. Previous studies have provided evidence on application of acoustical methods for estimation of AHI and sleep apnea monitoring at home. However, a challenge for current acoustical sleep screening devices is the lack of airflow estimation and presentation for assessment of respiratory events by physicians. Our extensive research has shown that tracheal signals can be used to provide a holistic solution for sleep screening at home. Also, analysis of tracheal signals suggests more convenient sleep monitoring especially in high risk patient populations, such as those who may require frequent assessment of their sleep, or cannot tolerate multiple sensor attachment, such as older individuals and children. Therefore, tracheal signals can provide a robust portable device to improve sleep apnea screening.

Pre-symptomatic detection of COVID-19 from physiological data measured during sleep via wearable sensor

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Abstract—**Wearable devices digitally measuring vital signs have been used for monitoring health and illness onset and have a high potential for real-time monitoring and disease detection. As such, they are potentially useful during public health crises, such as the current COVID-19 global pandemic. In my talk, I'll discuss how wearables biosensors can be used as a tool to early detect COVID19 onset using heart rate, activity, and sleep data. By using retrospective smartwatch data, we showed that 63% of the COVID-19 cases could be detected before symptom onset in real-time via the occurrence of extreme elevations in resting heart rate relative to the individual baseline. Sleep features are perturbed around infection time and days before patients develop symptoms. Our findings suggest that consumer wearables may be used for the large-scale real-time detection of respiratory infections, often pre-symptomatically, and provide an approach for managing epidemics using digital tracking and health monitoring.**

V. INTRODUCTION

The use of wearable devices has ample potential to mitigate the coronavirus disease 2019 (COVID-19) pandemic. To date, the pandemic has infected two hundred million individuals and caused over 2 million deaths worldwide (https://covid19.who.int). There is a substantial need for improved infection tracking, and population-scale technology solutions provide a promising avenue to identify cases in real-time for infection detection and tracking [1]. Using heart rate data from a large cohort of individuals, we showed that heart rate signals from fitness trackers can be used to retrospectively detect COVID-19 infection well in advance of symptom onset [2]. In this talk, the effect of SARS-CoV-2 on sleep will be discussed.

VI. METHODS

We recruited participants with a confirmed or suspected COVID-19 infection, as well as those at high risk of exposure to COVID-19, individuals with unknown respiratory illness and individuals who did not report any illness. Participants were asked to wear their fitness tracker daily, as much as possible, and to download a study app called MyPHD with which to share their wearable device data. Thirty-two COVID-19-positive participants had Fitbit data spanning and adjacent to the COVID-19 disease dates, as well as symptom dates and diagnosis dates. Using the Resting Heart Rate difference (RHR-Diff) method [2], we detected and identified elevated RHR time intervals based on the standardized residuals. Our sleep analysis only considered individuals who had detectable changes in their RHR between -14 days before symptom onset and 2 days after, using our RHR-Diff algorithm [2]. We also removed individuals with more than 50% of sleep (each individually) data missing in a window of 21 days before symptom onset and 7 days after. This resulted in 13 individuals for the sleep analysis. Following this filtration criteria, missing values were imputed using the last observation carried forward (LOCF) method. Afterward, total sleep duration was Z-normalized for each person independently. LMMs were conducted for all sleep parameters using the nlme package (version 3.1-142) in R. In our model, we included day annotation as a fixed effect and subject ID as a random effect. An analysis of variance test was applied on the fitted model to retrieve a p-value for the tested hypothesis.

VII. RESULTS AND DISCUSSION

We investigated whether the onset of COVID-19 affected behavior, specifically sleep. Out of 12 extracted sleep features, we found that sleep duration significantly increased after the onset of the outlying RHR signal (LMM; $P = 0.003$). These results indicate that COVID-19 illness alters sleep patterns, which can be tracked using a wearable device.

ACKNOWLEDGEMENT

REFERENCES

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[2] T. Mishra, M. Wang, A.A. Metwally, G. K. Bogu, *et al*. Pre-symptomatic detection of COVID-19 from smartwatch data. *Nature Biomedical Engineering*. 2020 4(12), 1208-1220.

Synopsis of Talk #4:

Predicting likelihood of future vaso-occlusive pain crises in sickle-cell disease from photoplethysmogram patterns measured during sleep

**Michael C.K. Khoo, Yunhua Ji, Patjanaporn Chalacheva,
and Thomas D. Coates**

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Transient surges in sympathetic activity generally accompany the arousals and limb movements that occur in obstructive sleep apnea and periodic leg movement disorder, both of which are common in sickle cell disease (SCD). We believe that these sympathetic surges lead to peripheral vasoconstriction that reduce microvascular blood flow and increase the likelihood of triggering painful vaso-occlusive crises (VOC) that are the hallmark of SCD [1]. This hypothesis is supported by our recent published report of a significant association between the magnitude of vasoconstriction, inferred from the finger photoplethysmogram (PPG) during sleep, and the frequency of future VOC in 212 children with SCD [2].

However, 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. In this talk, we will present further new results that help to explain why this is the case.

As well, we present an improved data-driven predictive model of VOC frequency that incorporates more detailed features extracted from the PPG signals in the same database. Briefly, we built a two-level stacking machine learning (ML) model for this purpose. The first level contains seven different base ML algorithms predicting each subject's pain category based on the input PPG characteristics and other clinical information, while the second level is a meta model which uses the inputs to the first-level model along with the outputs of the base models to produce a final prediction. Model performance in predicting future pain frequency was significantly higher than in predicting pain frequency prior to each subject's sleep study (F1-score 0.4255 vs 0.3505, p-value < 0.0001), consistent with our hypothesis of a causal relationship between vasoconstriction and future pain incidence, rather than past pain leading to greater propensity for vasoconstriction . The model also performed much better than the predictions made using our previous statistical model (F1 0.3279), as well as all other algorithms that used only the base-model outputs for predicting pain outcomes without the second tier meta model.

Our studies represent the first attempt ever to use noninvasively measured signals during sleep to predict future likelihood for VOC crises in SCD patients. Since the primary signal input is derived from finger PPG, our efforts are now aimed at addressing the future possibility of deploying an improved version of our algorithms in a low-cost wearable system that can assist clinicians in managing long-term therapy for SCD patients.

REFERENCES

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