

Unveiling the Impact of Respiratory Event-Related Hypoxia on Heart Sound Intensity During Sleep Using Novel Wearable Technology

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Purpose: Cardiovascular disorders are the leading cause of mortality worldwide with obstructive sleep apnea (OSA) as the independent risk factor. Heart sounds are strong modalities to obtain clinically relevant information regarding the functioning of the heart valves and blood flow. The objective of this study was to use a small wearable device to record and investigate the changes in heart sounds during respiratory events (reduction and cessation of breathings) and their association with oxyhemoglobin desaturation (hypoxemia).

Patients and Methods: Sleep assessment and tracheal respiratory and heart sounds were recorded simultaneously from 58 individuals who were suspected of having OSA. Sleep assessment was performed using in-laboratory polysomnography. Tracheal respiratory and heart sounds were recorded over the suprasternal notch using a small device with embedded microphone and accelerometer called the Patch. Heart sounds were extracted from bandpass filtered tracheal sounds using smoothed Hilbert envelope on decomposed signal. For each individual, data from 20 obstructive events during Non-Rapid Eye Movement stage-2 of sleep were randomly selected for analysis.

Results: A significant increase in heart sounds' intensities from before to after the termination of respiratory events was observed. Also, there was a significant positive correlation between the magnitude of hypoxemia and the increase in heart sounds' intensities ($r > 0.82$, $p < 0.001$). In addition, the changes in heart sounds were significantly correlated with heart rate and blood pressure.

Conclusion: Our results indicate that heart sound analysis can be used as an alternative modality for assessing the cardiovascular burden of sleep apnea, which may indicate the risk of cardiovascular disorders.

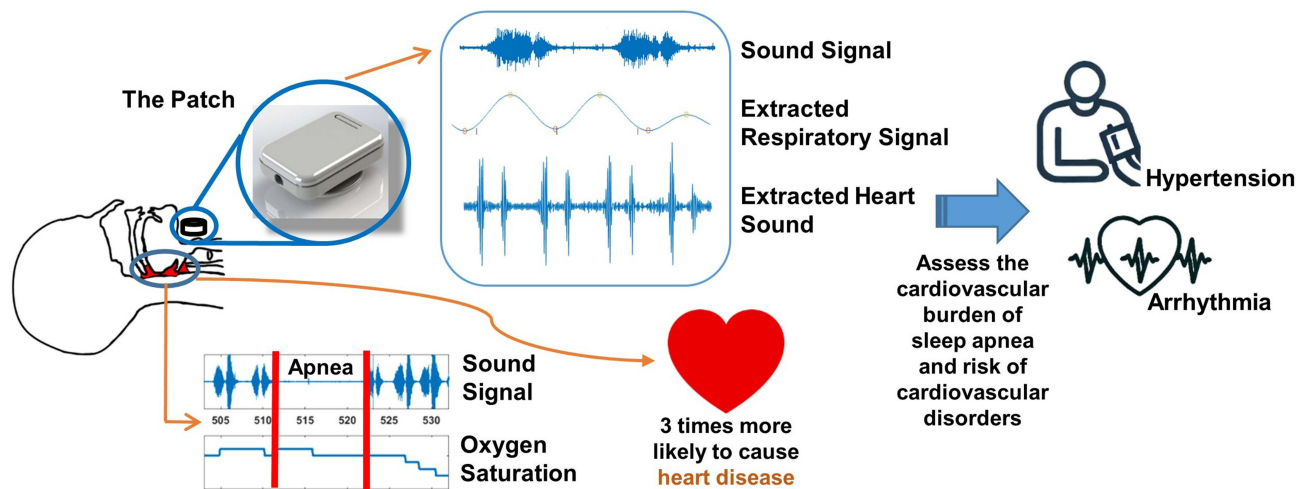
Keywords: heart sounds, obstructive sleep apnea, sympathetic nervous activity, hypoxemia, blood pressure

Introduction

Cardiovascular disorders are the leading cause of mortality and morbidity worldwide¹ with obstructive sleep apnea (OSA) being an independent risk factor.^{2,3} OSA is a common breathing disorder marked by recurring episodes of breath cessation (apnea) or reduction (hypopnea) during sleep, resulting from complete or partial closure of the pharyngeal airway. The prevalence of OSA in patients with hypertension and congestive heart failure are 35%⁴ and 80%,⁵ respectively, exceeding the 10% prevalence in general population.⁶

OSA adversely impacts the autonomic nervous system, altering heart rate regulation due to increased activity of the sympathetic nervous system.^{7,8} Other factors contributing to the cardiovascular consequences of OSA include heightened negative intrathoracic pressure during apneas and hypopneas, increased sympathetic nervous system activity caused by oxyhemoglobin desaturation (hypoxemia),⁹ and the resulting spikes in blood pressure and heart rate at the termination of these episodes.¹⁰

Graphical Abstract



The response of the cardiovascular system to individual respiratory events during sleep is affected by several factors such as associated hypoxemia, presence of arousals, and the frequency of apneas and hypopneas per hour of sleep known as the apnea-hypopnea index (AHI).¹¹ Higher AHI is known to be associated with increased risk of cardiovascular disease. Moreover, the hypoxic burden, which quantifies the area under the curve of overnight oxygen desaturations that are associated with sleep apnea has been shown to predict cardiovascular events and mortality in patients with OSA.^{12,13} However, the AHI alone lacks sufficient sensitivity and specificity to predict cardiovascular events¹⁴ while the hypoxic burden is unable to distinguish between various patterns of hypoxic stress.¹² The current technologies for monitoring cardiac condition such as electrocardiogram (ECG), oxyhemoglobin saturation (SaO₂), or continuous blood pressure monitoring systems (such as Finapres) primarily provide information about electrical activity of the heart, oxygenation status, or information on systemic perfusion. However, they are unable to comprehensively capture the mechanical aspects of cardiac activity, which is important to detect early valvular abnormalities, and its response to apneas and hypopneas. Therefore, there is a need for an alternate metric or tool that can be useful in assessing and predicting the pathophysiology of cardiovascular diseases in individuals with OSA.^{12,14}

Heart sounds (S1 and S2) provide clinically relevant insights into heart valve function and blood flow dynamics. The first heart sounds, S1, results from the closure of the mitral and tricuspid valves at the onset of isovolumetric ventricular contraction. Meanwhile, the second heart sound, S2, is generated by the closure of the aortic and pulmonic valves at the start of isovolumetric ventricular relaxation. In our proof-of-concept study ([Appendix 1](#)), we showed that the changes in heart sound intensities were correlated with the changes in systolic and diastolic blood pressures ([Supplementary Figure 1A–C](#)). Moreover, earlier research indicates that accurately identifying each component of heart sounds yields valuable insights for predicting cardiovascular disorders.^{15–17} Crucially, heart sounds can be continuously and easily recorded using a microphone placed on the chest or neck, causing minimal discomfort to the participants. Although heart sounds have clear potential for assessing cardiovascular disorder pathology, no convenient tool currently exists to monitor the cardiovascular effects of OSA during sleep based on heart sounds. Therefore, the goal of this study was to investigate the potential of a device developed in our lab based on heart sounds in assessing the cardiovascular consequences of OSA during sleep. To achieve this goal, our objectives were 1) to develop a technique to extract heart sounds from the recorded sounds in the presence of noise such as snoring and 2) to investigate the effects of apneas and hypopneas on the intensities of heart sounds S1 (HSI_{S1}) and S2 (HSI_{S2}) compared to normal breathing.

We hypothesized that, from pre-termination to post-termination of respiratory events, there would be increases in HSI_{S1} and HSI_{S2}. In addition, we hypothesized that the changes in HSI_{S1} and HSI_{S2} from pre-termination to post-



termination of respiratory events were correlated with the magnitude of physiological derangement such as hypoxemia during the events and changes in heart rate and blood pressure.

Materials and Methods

This was a prospective observational cohort study. The study complies with the Declaration of Helsinki and was approved by the research ethics board of the University Health Network. All participants were fully informed about the purpose of the study and signed written consent prior to participation in the study.

Participants

Participants of 18 years and older with suspected OSA who were referred to the sleep laboratory of Toronto Rehabilitation Institute¹⁸ for overnight PSG were recruited for this study. Participants whose skin was sensitive to medical tapes were excluded. In addition, we had the following exclusion criteria for the data analysis: 1) participants with low quality data (signal to noise ratio below 20 for acoustic data), 2) participants with no OSA who had less than 5 obstructive respiratory events during Non-Rapid Eye Movement stage-2 (N2) due to insufficient data for a meaningful analysis, 3) participants with no hypoxemia during sleep (no drops in SaO₂ of at least 3%), and 4) participants who had atrial fibrillation on the night of the study as the irregular rhythm can disrupt the characteristics of heart sounds that would make it difficult to interpret the results.

Data Acquisition

Overnight Polysomnography (PSG)

A comprehensive overnight PSG was conducted using Embla[®] N7000/S4500 (Natus Medical Incorporated, USA). The PSG recorded cardiac function (ECG), brain activity (electroencephalogram, EEG), muscle activity (electromyogram, EMG), respiration (chest and abdominal respiratory inductance plethysmography), airflow (nasal pressure cannula), and blood oxygen saturation (SaO₂ via pulse oximetry). Apneas, hypopneas, sleep stages, and arousals were identified and scored according to the American Academy of Sleep Medicine guidelines.¹⁹ Apneas were defined as a reductions in airflow or abdominal and chest movement of over 90% for at least 10 seconds. Hypopneas were classified as a reduction in airflow or abdominal and chest movement of over 30% for more than 10 seconds, accompanied by arousals or at least a 3% drop in SaO₂.¹⁹ (see [Appendix 2](#)).

Tracheal Sounds Recording

Tracheal sounds, consisting of respiratory and heart sounds, were recorded continuously and simultaneously with the PSG using a small wearable device (The Patch) developed in our laboratory.^{20–23} The Patch consisted of a microphone and an accelerometer to record sounds and body movement, respectively. The Patch was secured to participants' suprasternal notch using double-sided tape ([Figure 1](#)). Custom hardware was developed to synchronize the Patch data with the PSG.

Signal Processing

Signal processing algorithms were developed using Matlab (2018a, MathWorks, Natick, MA).

Electrocardiogram Processing

The ECG recording from the overnight PSG was sampled at 250Hz. Parabolic fitting was utilized to identify the R-peaks in the ECG.²⁴ Subsequently, the R-R time series were averaged over 10-second intervals to establish the gold standard heart rate (HR_{ECG}).

Heart Sound Localization from the Tracheal Sound Recording

Sounds recorded over the trachea include normal breathing, snoring, and heart sounds. To extract the features of the heart sounds, several steps were undertaken to eliminate noise, including snoring.

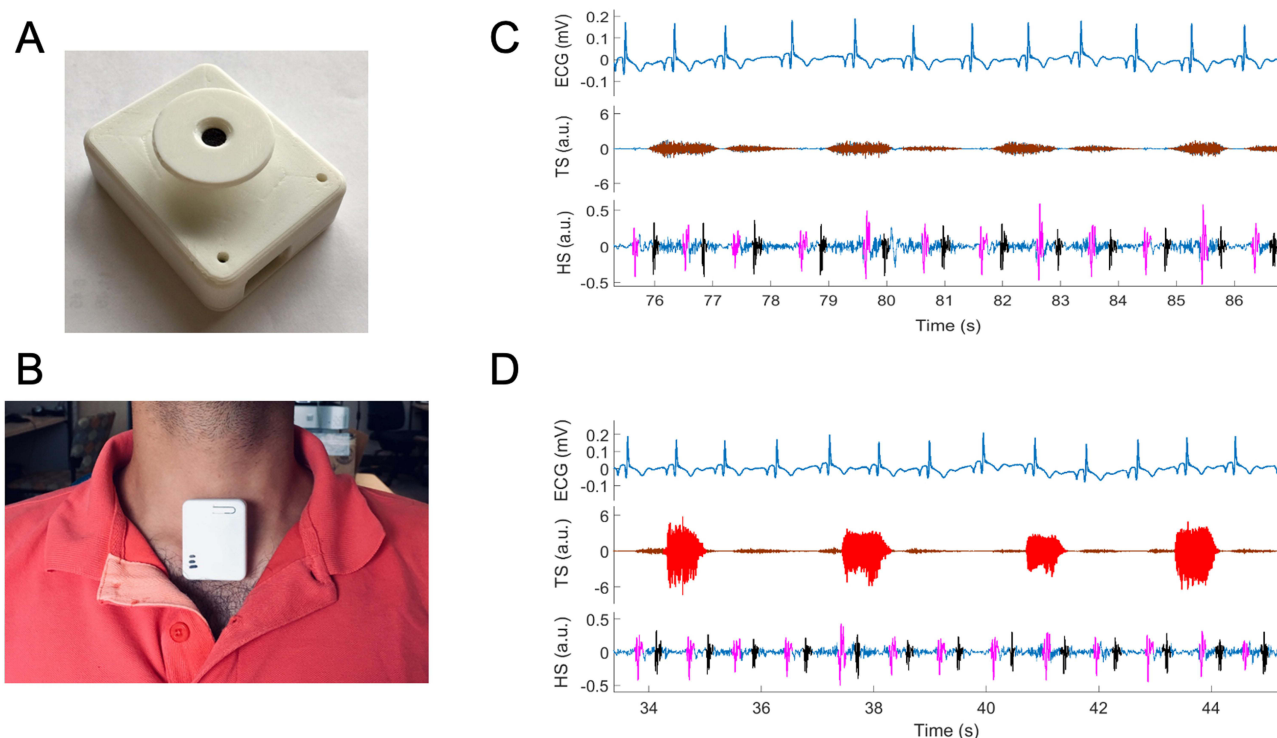


Figure 1 Extraction of heart sounds (HS), S1 (marked as pink) and S2 (marked as black) from tracheal sound (TS) recorded by the Patch (A) attached to participant's suprasternal notch (B) during (C) normal breathing and (D) snoring (shaded red in TS). ECG is recorded from PSG. Tracheal sound containing segments of either (C) normal breathing (marked as brown in TS representing inhalation and exhalation) or (D) snoring (marked as red).

Detection of snoring sound

Snoring sounds span a broad frequency spectrum of 20–2000Hz,²⁵ overlapping with the 10–250Hz range of heart sounds.²⁶ Importantly, the higher intensity of snoring sounds often obscures heart sounds. Therefore, it is necessary to identify snoring sounds and apply suitable filtering to accurately locate heart sounds. Accordingly, tracheal sounds were bandpass filtered with a cut-off frequency range of 200–2000Hz. Using a moving window, features from the sound and respiratory-related body movements were computed. Finally, the snoring segments were identified through a weighted average of features' scores derived using adaptive thresholds (details in [Appendix 3](#)).

Estimation of heart rate from heart sound

The tracheal sound recorded by the Patch was bandpass filtered using 20–150Hz cut-off to eliminate breathing sounds²⁷ and high-frequency background noise. For segments containing snoring sounds, the first intrinsic mode function was extracted using empirical mode decomposition²⁸ and subtracted from the filtered sound to isolate heart sounds. Then, the Hilbert envelope was computed and smoothed using a low-pass Butterworth filter at a 7Hz cut-off. Finally, the subsequent peaks of the smoothed Hilbert envelope were identified as the S1 and S2 heart sounds ([Figure 1](#)). The S1-S1 time series were generated and averaged over 10-second intervals to estimate heart rate from the heart sounds (HR_{HS}).

Analysis of Changes in Heart Sound Intensities During Respiratory Events and Normal Breathing

For each participant, 20 obstructive apneas/hypopneas during N2 sleep stage, as marked by the sleep technicians, were randomly selected in order to perform consistent comparison. In this study, only N2 sleep stage was considered as it is the most prevalent sleep stage and may also have a greater impact on the cardiovascular system. In participants with no-OSA, who may have less than 20 events, a minimum of 5 events during N2 sleep stage was considered. For each respiratory event, three 10-second segments were extracted ([Figure 2](#)): 1) *pre-event*: before the start of the event; 2) *pre-termination*: before the onset of arousal or termination of the respiratory event in case of no arousal; and 3) *post-termination*: after the arousal or termination of the event in case of no arousal. Then, for each segment, the average area

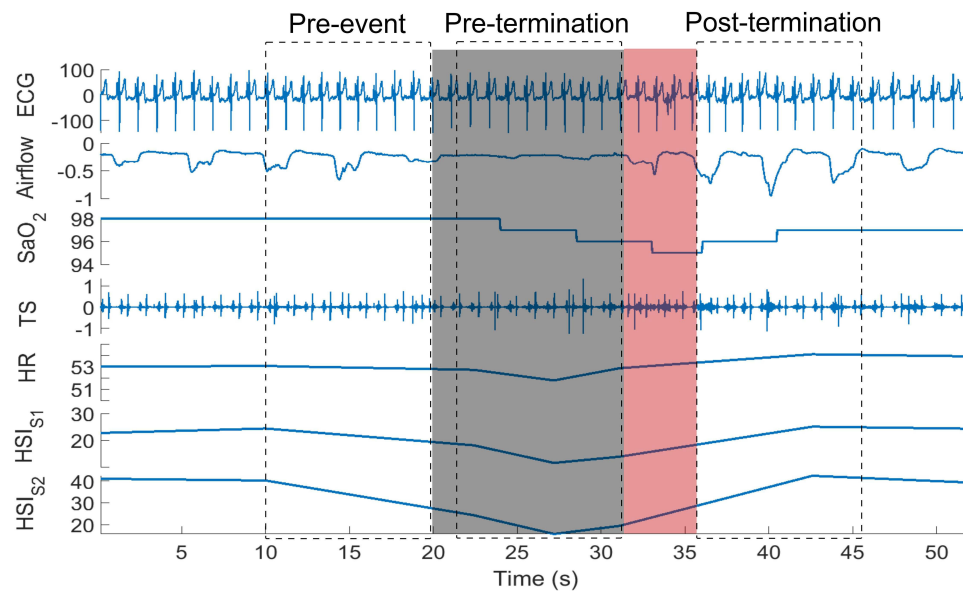


Figure 2 An extracted hypopnea and the segments of the data considered for heart rate and HSI analysis. The gray shaded area shows hypopnea and the red shaded area indicates the arousal. The dotted rectangles represent the 10-second pre-event, pre-termination and post-termination segments considered for our analysis.

Abbreviations: ECG, electrocardiogram (mV); SaO₂, oxygen saturation (%); TS, tracheal sound; HR, heart rate (bpm); HSI_{S1}, S1 intensity (db); HSI_{S2}, S2 intensity (db).

under the curve of the detected S1 and S2 envelopes were calculated as the averages of HSI_{S1} and HSI_{S2}, respectively. Also, the average HR_{HS} were extracted. Subsequently, the changes in HR_{HS}, HSI_{S1} and HSI_{S2} among the three selected segments were calculated for each event. The magnitude of hypoxemia was defined as the total drop in SaO₂ level during each respiratory event. In addition, for each participant, 20 normal breathing epochs with duration of 30 seconds were selected randomly to investigate the relationship between heart rate calculated from ECG (HR_{ECG}) and heart sound intensities (HSI_{S1} and HSI_{S2}).

Sex-Based Analyses of Changes in Heart Rate and Heart Sound Intensities During Respiratory Events

Participants were separated into male and female category. For each participant, the average changes in HR_{HS}, HSI_{S1} and HSI_{S2} were calculated for each category of drop in SaO₂ level during each respiratory event while ignoring the arousal intensity.

Effects of Arousal Intensity on Heart Rate and Heart Sound Intensities

Since arousals can influence heart sounds, the respiratory events were dichotomized into events that terminated a) with arousals; and b) without arousals. For events that terminated with arousals, their intensity was estimated using a modified version of the method proposed by Azarbarzin et al²⁹ using electroencephalogram signal (details in [Appendix 4](#)). To investigate the correlation between the changes in HR_{HS}, HSI_{S1}, and HSI_{S2} from pre-termination to post-termination of respiratory events and arousal intensity, two sound segments were extracted for each arousal:²⁹ i) 10-second segment ending at 2 seconds before arousal onset and ii) the segment from arousal onset until 8 seconds after the arousal end.

Statistical Analysis

For statistical analyses, the RStudio version 1.3.1056 was used. Participants were categorized into four groups based on sleep apnea severity: a) No-OSA (AHI≤5), b) Mild-OSA (5<AHI≤15), c) Moderate-OSA (15<AHI≤30), and d) Severe-OSA (AHI>30). Based on the Shapiro–Wilk normality test, one-way ANOVA or Kruskal Wallis test was used to assess the differences between demographics and sleep-related features among participants with different OSA severity. For categorical features χ^2 test was used. Pearson's correlations were applied to evaluate the relationships between HR_{HS} and HR_{ECG} for data with a normal distribution, while Spearman correlation was used for non-normally distributed data.

Additionally, the root-mean-square-error (RMSE) between HR_{HS} and HR_{ECG} was computed for each sleep stage and position.

A one-way ANOVA was employed to analyze the influence of breathing patterns (normal breathing during wakefulness and sleep, and snoring) on heart rate estimation. To evaluate the effects of sleep stages and sleep positions on heart rate estimation, a two-way repeated measures ANOVA was used. In addition, based on normality test, differences in HSI_{S1} and HSI_{S2} from pre-event to pre-termination and post-termination were compared using Friedman or repeated measure ANOVA tests, respectively. Post-hoc analysis was performed using Friedman Conover test or paired *t*-test with an adjusted *p*-value for non-normal and normal data, respectively. Repeated measure correlation was used to assess the relation between drop in SaO_2 and HR_{HS} , HSI_{S1} , and HSI_{S2} for events terminated with or without arousals. Linear mixed model with repeated measure was used to assess the changes in HR_{HS} , HSI_{S1} , and HSI_{S2} between events with and without arousals, for different levels of drop in SaO_2 .

To study the effect of arousal intensity and drop in SaO_2 on HR_{HS} , HSI_{S1} , and HSI_{S2} , a linear mixed model with repeated measure was used. Similarly, the changes in HSI_{S1} and HSI_{S2} (ΔHSI_{S1} and ΔHSI_{S2}) with respect to drop in SaO_2 were compared using linear mixed model with repeated measure for subjects with OSA severity of $AHI > 30$ only. We could not run the analysis for other OSA severity categories due to the limited number of data points for some of the hypoxemia levels. Finally, to assess the interaction between arousal intensity and drop in SaO_2 levels, a multivariate linear mixed model with repeated measure was used. A *p*-value of < 0.05 was considered statistically significant.

Results

Out of 121 participants aged 18 years and above who were screened for eligibility, 95 individuals agreed to participate in the study. We excluded 5 participants for low-quality data and 13 participants for having less than five obstructive events during N2 stage of sleep. Furthermore, we excluded 13 participants whose overnight drops in SaO_2 values for all events were less than 3% (6 individuals) or more than 9% (7 individuals), as there were not enough statistical power for fair comparison. Subsequently, data from 58 participants were included in this study. The average age, BMI, and AHI of the participants (25 females) were 54.7 ± 13.5 years, 30.5 ± 7.1 kg/m², and 33.2 ± 25.7 events/hour, respectively.

Demographic and sleep data are presented in Table 1. Three participants had No-OSA, 12 had Mild-OSA, 19 had Moderate-OSA, and 24 had Severe-OSA. Age and BMI were significantly different between the four subgroups ($p = 0.012$, 0.008 , respectively). Also, the average and minimum SaO_2 were significantly different between the four OSA groups ($p = 0.032$, < 0.001 , respectively). However, sleep efficiency was not significantly different between the four OSA subgroups ($p = 0.955$). As expected, the number of arousals per hour of sleep was significantly higher in participants with severe OSA (53.7 ± 24.7 events/h) compared to those with moderate (26.4 ± 11.8 events/h, $p < 0.001$), mild (19.2 ± 4.8 events/h, $p < 0.001$) and no (12.7 ± 3.4 events/h, $p < 0.01$) OSA.

Table 1 Demographic Data and Overnight Polysomnography Findings in Different Groups of OSA Patients

		Total	$AHI \leq 5$	$5 < AHI \leq 15$	$15 < AHI \leq 30$	$AHI > 30$	<i>p</i> -value
Demographic	N (Female)	58 (25)	3 (2)	12 (6)	19 (8)	24 (9)	0.747
	Age (yrs)	54.7 ± 13.5	$32.3 \pm 16.4^{**}$	55.5 ± 13.4	53.1 ± 10.4	58.5 ± 13.2	0.012*
	BMI (kg/m ²)	30.5 ± 7.1	37.5 ± 7.8	26.7 ± 4.2	28.9 ± 6.4	32.9 ± 7.5	0.008*
	Weight (kg)	195.1 ± 51.3	237.5 ± 62.4	168.4 ± 30.4	183.8 ± 44.1	212.0 ± 56.6	0.018*
	Height (cm)	169.8 ± 9.7	168.9 ± 5.8	169.1 ± 7.4	169.6 ± 8.1	170.5 ± 12.2	0.977
Sleep Structure	History or CVD (Female)	16	0	2 (0)	6 (2)	8 (3)	—
	AHI (events/hr)	33.2 ± 25.7	$4.2 \pm 1.0^{**}$	$9.4 \pm 3.4^{**}$	$21.9 \pm 4.2^{**}$	$57.7 \pm 21.9^{**}$	$< 0.0001^*$
	Sleep efficiency (%)	77.4 ± 15.7	83.0 ± 7.4	77.7 ± 12.7	76.8 ± 17.0	77.2 ± 17.2	0.955
	Mean SaO_2 (%)	93.8 ± 2.7	94.9 ± 1.0	94.7 ± 2.4	94.7 ± 1.7	92.5 ± 3.2	0.032*
	Minimum SaO_2 (%)	81.9 ± 8.1	86.7 ± 6.8	87.7 ± 5.6	83.5 ± 4.7	77.2 ± 8.9	$< 0.001^*$
	Arousal Index (events/hr)	35.5 ± 23.4	12.7 ± 3.4	19.2 ± 4.8	26.4 ± 11.8	$53.7 \pm 24.7^{**}$	$< 0.0001^*$

Notes: Data are presented as mean \pm standard deviation. Bold text indicates significant changes; *indicate statistically significant changes between groups. **indicate statistically significant changes of that group with all other groups.

Abbreviations: N, Number; BMI, Body Mass Index; AHI, Apnea Hypopnea Index; CVD, Cardiovascular disease.

Heart Rate Estimation from Heart Sound

In all participants, strong correlations between HR_{ECG} and HR_{HS} were observed across all sleep stages and positions ($r > 0.92$, $p < 0.001$, in every case) – thus indicating that the heart sounds corresponding to the ECG beats were localized with high precision. During wakefulness, normal breathing while asleep and snoring, the mean RMSE between HR_{ECG} and HR_{HS} were 2.9 beat per minute (bpm), 1.7bpm and 2.5bpm, respectively (Table 2). A two-way repeated measures ANOVA revealed that sleep position had a marginal effect on the RMSE of HR_{HS} estimation ($p = 0.07$). However, sleep stage significantly impacted the RMSE of HR_{HS} estimation ($p < 0.001$). Post-hoc analysis indicated that, for both supine and lateral positions, the HR_{HS} estimation error was significantly higher during wakefulness than across various sleep stages ($p < 0.001$).

Changes in Heart Sound Intensity with Respect to Respiratory Events in Overnight Data

There were significant increases in post-termination HSI_{S1} and HSI_{S2} relative to the pre-termination and pre-event HSI_{S1} and HSI_{S2} (Figure 3A, HSI_{S1} : 26.9 ± 0.752 dB vs 24.7 ± 0.909 dB, $p < 0.0001$ and 25.7 ± 0.518 dB, $p < 0.001$; Figure 3B, HSI_{S2} : 23.2 ± 0.828 dB vs 20.4 ± 0.714 dB, $p < 0.0001$ and 22.1 ± 0.515 dB, $p < 0.0001$). In addition, the pre-termination HSI_{S1} and HSI_{S2} were significantly lower than the pre-event HSI_{S1} and HSI_{S2} ($p < 0.0001$; Figure 3A and B).

In all subjects, there were significant positive correlations between HR_{ECG} and HSI_{S1} during respiratory events ($r = 0.49$ – 0.60 , $p < 0.001$) and normal breathing ($r = 0.47$ – 0.58 , $p < 0.01$). On the other hand, the correlation between HR_{ECG} and HSI_{S2} was only significant during respiratory events ($r = 0.38$ – 0.45 , $p < 0.05$), but not during normal breathing ($p > 0.3$).

From pre-termination to post-termination of respiratory events with or without arousals, the changes in HR_{HS} , HSI_{S1} and HSI_{S2} were significantly correlated with the associated drops in SaO_2 , with the highest change being for 9% drop compared to 3% drop in SaO_2 (Figure 4A–F).

The association of drops in SaO_2 with changes in HR_{HS} ($p < 0.05$), HSI_{S1} ($p < 0.001$), and HSI_{S2} ($p < 0.001$) were significant even after including arousal intensity in the linear mixed model with repeated measures. However, for the same level of hypoxemia, the changes in HR_{HS} , HSI_{S1} , and HSI_{S2} from pre-termination to post-termination were not significantly different for respiratory events that terminated with arousals compared to those that were terminated without arousals (Figure 5A–C).

Finally, for participants with $AHI > 30$, the changes in HSI_{S1} and HSI_{S2} from pre-termination to post-termination events were significantly different ($p < 0.001$) among events with different hypoxemia levels (Figure 6). For other OSA severity categories, we could not run the analysis due to the limited number of data points in some of the hypoxemia levels. Participants with a previous history of cardiovascular conditions showed a trend of larger increases in HSI_{S2} from pre-termination to post-termination events, compared to those with no known history (Figure 7A and B).

Table 2 Comparison of the Effect of Sleep Position, Sleep Stages, Normal Breathing and Snoring During Sleep on the Root-Mean-Square-Error (RMSE) in Heart Rate Estimation from the Patch

Sleep Position	Sleep Stages				
	Awake	N1	N2	N3	REM
Supine, bpm	2.83±0.1*	1.86±0.06	1.82±0.01	1.77±0.04	1.95±0.09
Lateral, bpm	2.91±0.1*	1.93±0.08	1.88±0.05	1.86±0.09	2.41±0.11
	Awake	Sleep			
		Normal breathing		Snoring	
All postures, bpm	2.86±0.1*	1.71±0.07		2.45±0.12	

Notes: Bold text indicates significant changes. Here, * = $P < 0.001$, showing statistically significant changes of that stage with all other sleep stages.

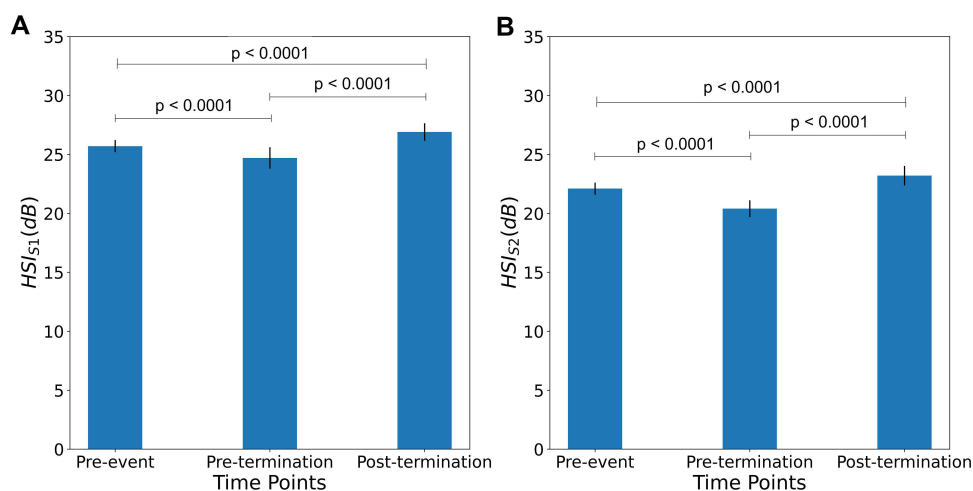


Figure 3 Differences in heart sound intensity HSI_{S1} (A) and HSI_{S2} (B) from pre-event to pre-termination and post-termination (N= 58): A significant increase in post-termination HSI_{S1} and HSI_{S2} can be observed as compared to pre-termination HSI_{S1} and HSI_{S2}, and pre-event HSI_{S1} and HSI_{S2}. Similarly, the pre-event HSI_{S1} and HSI_{S2} were significantly higher compared to pre-termination HSI_{S1} and HSI_{S2}.

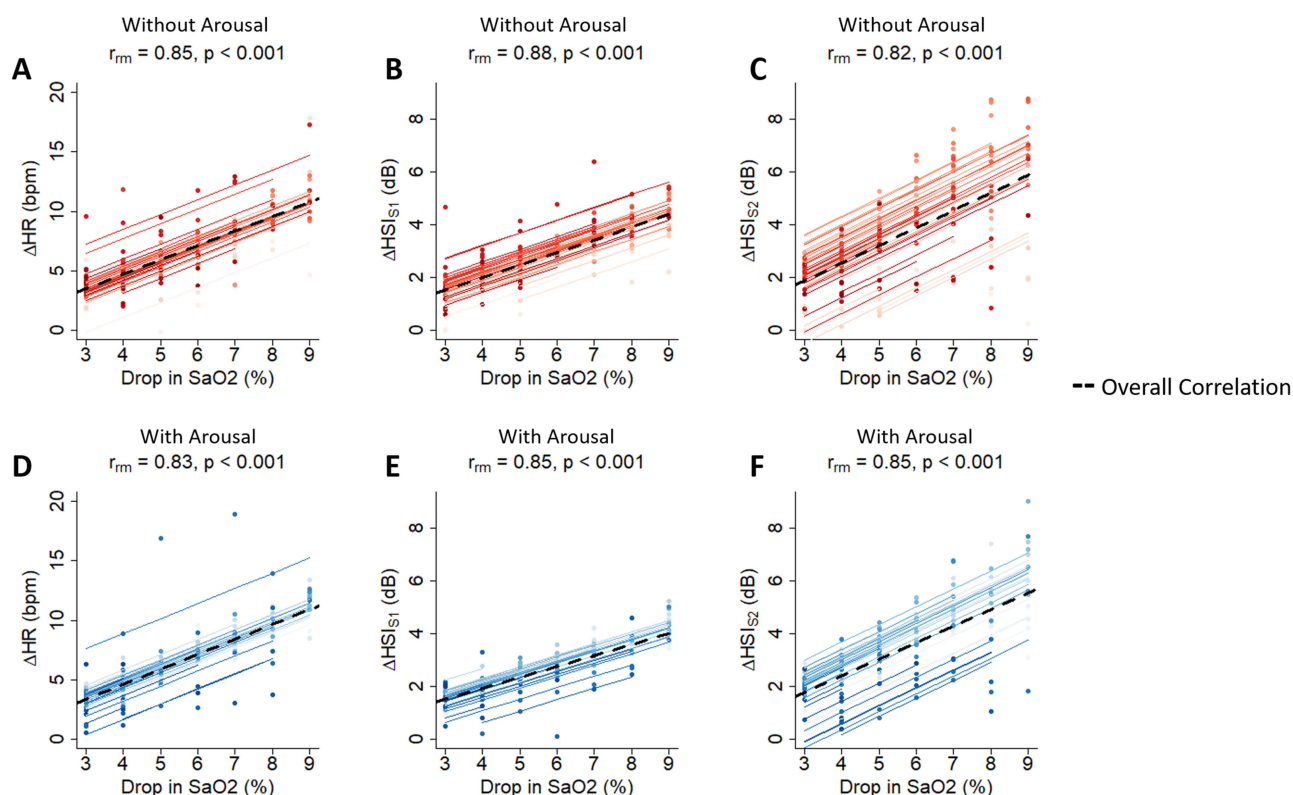


Figure 4 Relation between change in HR, HSI_{S1} and HSI_{S2} with drop in SaO₂ during events with and without arousals (N = 58). Significant positive correlations were observed between changes in HR, HSI_{S1} and HSI_{S2} with drop in SaO₂ for events without arousals (A–C) and for events with arousals (D–F). The dashed line in the figures shows the overall correlation.

Sex-Based Analysis

In each category (male and female), the changes in HR_{HS}, HSI_{S1} and HSI_{S2} were significantly correlated with the associated drops in SaO₂, with the highest change being for 9% drop compared to 3% drop in SaO₂ (Figure 8).

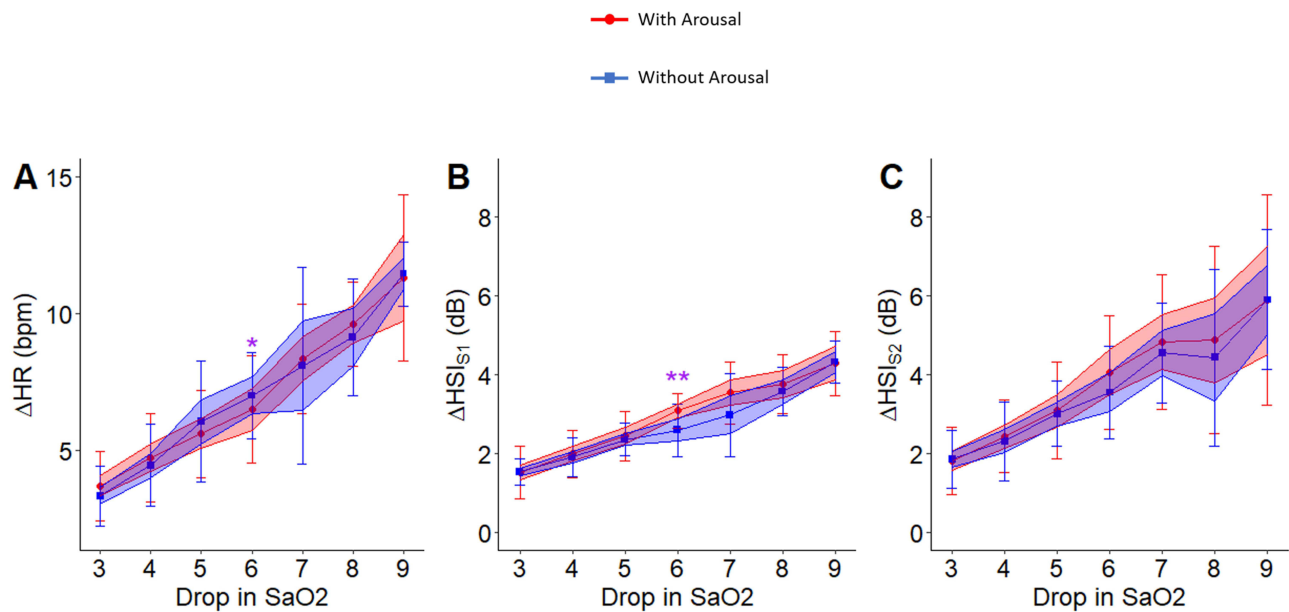


Figure 5 Relation between change in heart rate, HSI_{S1} and HSI_{S2} with drop in SaO_2 during events with and without arousals ($N = 58$). No significant differences in the associated change in heart rate (A), HSI_{S1} (B) and HSI_{S2} (C) with drop in SaO_2 were observed. For the hypoxemia level of 6%, the changes in HR_{HS} ($p < 0.05$) and HSI_{S1} ($p < 0.01$) were significantly different between events that terminated with arousals compared to those without arousals. Here, * indicates $p < 0.05$ and ** indicates $p < 0.01$. The color band shows the confidence interval of 0.95% and the bars indicate standard deviation.

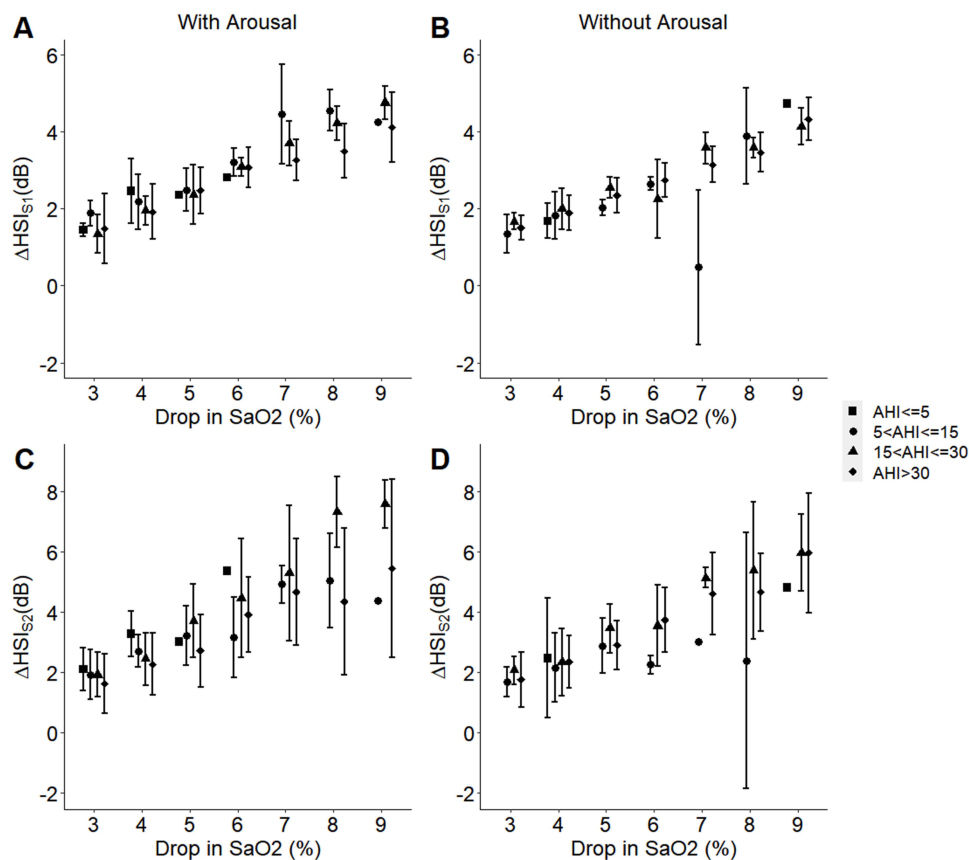


Figure 6 Effect of the participants' overall AHI on the changes in heart sound intensities HSI_{S1} and HSI_{S2} with hypoxemia in the presence (A and C) or absence (B and D) of arousal. For participants with $AHI > 30$ ($N = 24$), linear mixed model with repeated measure analysis indicated significant changes ($p < 0.001$) in HSI_{S1} and HSI_{S2} among events with different hypoxemia levels from pre-termination to post-termination events, which terminated with or without arousals. For other OSA severity categories, we could not run the analysis due to the limited number of data points in some of the hypoxemia levels.

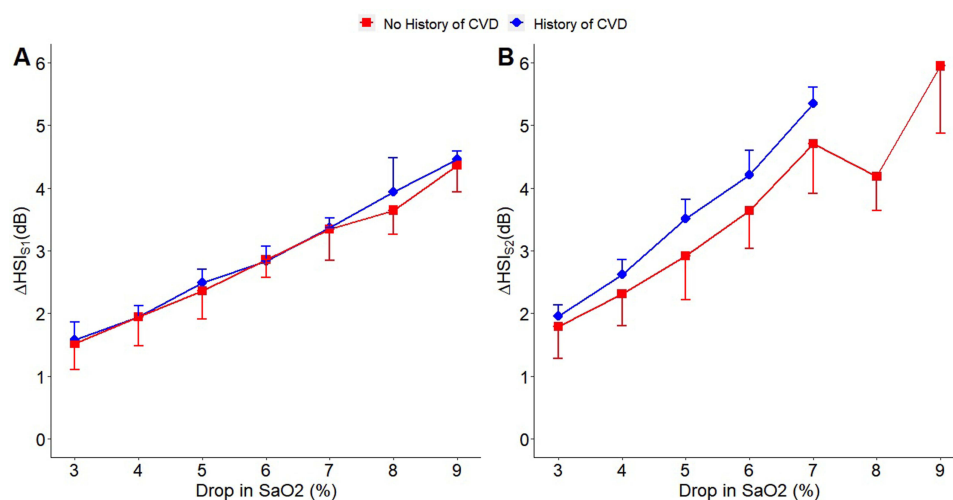


Figure 7 Effect of the participants' history of cardiovascular disease (CVD) on the changes in heart sound intensities HSI_{S1} (A) and HSI_{S2} (B) with hypoxemia (N = 16). A trend of larger increase in HSI_{S2} from pre-termination to post-termination event was observed in participants with previous history of cardiovascular disorder (CVD) compared to those with no known history.

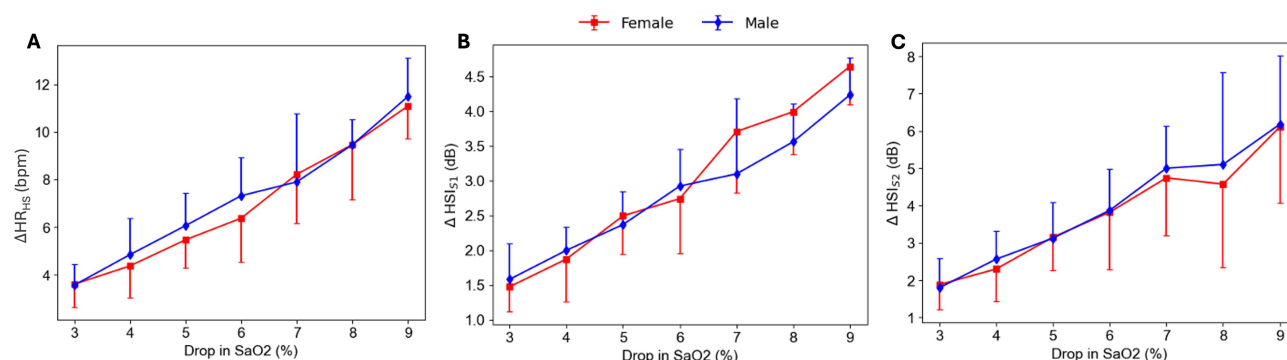


Figure 8 Sex-based analysis on the changes in heart rate extracted from heart sound HR_{HS} (A) and heart sound intensities HSI_{S1} (B) and HSI_{S2} (C) with hypoxemia. No significant differences in the changes in HR_{HS}, HSI_{S1} and HSI_{S2} from pre-termination to post-termination event between male and female participants was observed.

Arousal Intensity Analysis

The results of the linear mixed model with the repeated measures to assess the effects of arousal intensity and drops in SaO₂ on changes in HR_{HS}, HSI_{S1}, HSI_{S2} are presented in Table 3. The changes in HR_{HS}, HSI_{S1}, HSI_{S2} were significantly associated with drops in SaO₂. However, these changes were not associated with arousal intensity, and there was no interaction between arousal intensity and drops in SaO₂.

Discussion

In this study, we introduced a reliable technology to record and extract heart sounds during overnight sleep. The extracted heart sounds can be used for monitoring the mechanical function of the heart including heart rate and pathophysiologic derangement such as hypoxemia during respiratory events in patients with OSA. The major findings of the study are: (i) compared to pre-termination and pre-respiratory events, there was a significant increase in post-termination HSI_{S1} and HSI_{S2}; (ii) the changes in HSI_{S1} and HSI_{S2} from pre-termination to post-termination of respiratory events with or without arousals showed a significant positive correlation with the associated drops in SaO₂, and (iii) changes in HSI_{S1} and HSI_{S2} were significantly correlated with the relative changes in heart rate and blood pressure, respectively.

In this study we introduced a technique for extracting heart sounds during sleep even in the presence of snoring. The Patch, placed on the suprasternal notch, captures tracheal respiratory sounds, including heart sounds, breathing sounds,

Table 3 Results of the Linear Mixed Model with Repeated Measure for the Association of Changes in HSI_{S1} and HSI_{S2} with Drop in SaO₂ and Arousal Intensity

	Value	p-value
HR_{HS}		
Intercept	2.4013865	0.1918
Arousal Intensity	-0.5652032	0.1421
Drop in SaO ₂	0.7434912	0.0173
Arousal Intensity:Drop in SaO ₂	0.1020740	0.1089
HSI_{S1}		
Intercept	-0.7268695	0.2561
Arousal Intensity	0.1760824	0.1882
Drop in SaO ₂	0.5778194	0.0000
Arousal Intensity:Drop in SaO ₂	-0.0219941	0.3167
HSI_{S2}		
Intercept	-0.7489223	0.5361
Arousal Intensity	0.0810042	0.7479
Drop in SaO ₂	0.7039053	0.0006
Arousal Intensity:Drop in SaO ₂	-0.0038487	0.9254

Note: Bold text indicates significant changes.

snoring, and ambient noise. We developed a Hilbert transform-based method to localize heart sounds and estimate heart rate. The estimated heart rate was then validated by comparing it with the heart rate derived from the ECG, ensuring accurate heart sound localization during sleep. Our study is also the first to estimate heart rate from heart sounds during sleep. While previous studies demonstrated high accuracy in assessing heart rate during normal breathing,^{30–32} none has been validated or performed well in the presence of snoring. Our proposed method employs empirical mode decomposition to minimize the impact of snoring, allowing for accurate localization of heart sounds and estimation of heart rate.

Previous studies have indicated that increases in heart rate are strongly associated with the loudness of heart sound S1.^{33,34} However, the influence of heart rate changes on heart sound S2 remains unclear. We investigated the relationship between variations in beat-to-beat heart rate and HSI_{S1}, HSI_{S2} during respiratory events and normal breathing. As expected, heart rate showed a significant correlation with HSI_{S1} in both normal breathing and respiratory events. In contrast, HSI_{S2} was only associated with heart rate during respiratory events, not normal breathing. This may suggest that changes in blood pressure rather than heart rate at the termination of respiratory events,^{35,36} account for the observed increase in HSI_{S2}. This finding was further supported by our preliminary data in healthy subjects performing Mueller Maneuvers, showing a significant correlation between HSI_{S2} and blood pressure. Furthermore, this correlation aligns with previous finding by Turnbull et al,³⁷ that slight reductions in overnight blood pressure can reduce the risk of adverse cardiovascular events in patients with OSA.

In patients with severe OSA, the HSI increased from pre to post termination of the events and this increase was associated with the drops in SaO₂. Furthermore, our multivariate analysis for HSI suggested that there was no interaction between arousal intensity and the drops in SaO₂, indicating that drops in SaO₂ may play a bigger role in the increment of the HSI. During pharyngeal airway obstruction, intermittent hypoxemia elevates sympathetic nervous system activity, leading to increased blood pressure during the night and day.^{7,38,39} Furthermore, the heart rate following an obstructive respiratory event has been observed to increase in proportion to the event's severity.¹⁸ This suggests that the relative increases in blood pressure and heart rate due to hypoxemia could be responsible for the corresponding increases in HSI_{S1} and HSI_{S2} from pre-termination to post-termination of events.

Compared to those with no known history of cardiovascular disorders, participants with the previous history of cardiovascular disorders had a tendency for a larger increase in HSI_{S2} from pre-termination to post-termination of events in association with drops in SaO_2 . This could suggest that cardiovascular disorders such as hypertension may constitute louder heart sounds⁴⁰ in conjunction with hypoxemia. Moreover, in patients with OSA, both heart rate and blood pressure remain elevated during sleep and show a positive correlation with the severity of sleep apnea.^{41,42} As our sample size was small, the effects of OSA severity on the changes in heart sounds' features with respiratory events should be investigated in future studies.

There are several limitations to this study. Although our developed algorithm successfully retrieved heart sounds and heart rate during snoring, the effect of signal decomposition on the HSI_{S1} and HSI_{S2} during snoring has not been verified. It was assumed that the HSI_{S1} and HSI_{S2} were not significantly affected since, i) for snoring segments, only the first level of the decomposed signal was removed; ii) rather than the actual magnitude, we investigated the changes in HSI_{S1} and HSI_{S2} . We had to exclude participants with overnight SaO_2 drops less than 3% and greater than 9%, as the limited range of values in these participants may not provide sufficient variability, which would disproportionately influence and skew the results. Also, we had only 16 participants with a previously known history of cardiovascular diseases. Pathologic cardiac conditions can create abnormal heart sounds⁴⁰ and should be explored further. Moreover, future studies could include more subjects with different severities of OSA to investigate the effects of OSA severity on heart sounds during sleep. Furthermore, we recorded the heart sounds from the suprasternal notch. We acknowledge the fact that heart sounds recorded over the chest may result in different performance for heart sound localization. Moreover, we only considered the obstructive events in this study. A future study should investigate the effects of other types of respiratory events, such as central events, on heart sound intensity. Finally, our current dataset is limited in terms of sample size. Future studies are required to access our results in a larger population.

Conclusion

In conclusion, this study demonstrates that monitoring heart sounds during sleep can be a promising tool for assessing hypoxemia during the events and changes in heart rate in patients with OSA. Despite advances in the treatment and prevention of cardiovascular disorders, the incidences of cardiovascular-related deaths remain high in patients with OSA. Therefore, heart sounds analyses can be a strong modality in identifying the mechanisms underlying the development and progression of cardiovascular disorders in patients with OSA. This can lead to the development of convenient and accessible technologies which can help in more accurate monitoring, earlier diagnosis, risk prediction, and improved treatment of cardiovascular disorders.

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