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A comparison of hypoxic burden algorithms using three different methods for calculating baseline oxygen saturation for predicting cardiovascular death in the Sleep Heart Health Study

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***Abstract*— Respiratory event related oxygen desaturation area measures have recently shown merit as novel predictors of cardiovascular disease (CVD) outcomes. In this study, we investigate one such measure (hypoxic burden (HB)) and investigate how three different ways of calculating the SpO2 baseline of the HB algorithm impact its ability to predict cardiovascular mortality. The three baseline estimation steps include a pre-event baseline, a record-based baseline, and a fixed baseline. Pulse oximetry signals from the Sleep Heart Health Study and the corresponding CVD outcomes were analyzed. The performance of each baseline method was compared using adjusted Cox proportional hazard regression analysis. Results show that HB with the record-based baseline method returned the best performing results with a hazard ratio (HR) of 1.83 (95% CI: 1.03-3.27, p<0.05) in the fully adjusted model, compared to HB with the pre-event baseline method (HR: 1.60, 95%CI: 0.86-3.00, p>0.05) and HB with the fixed baseline method (HR: 1.73, 95%CI: 0.93-3.22, p>0.05).**

I. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide. Obstructive sleep apnoea (OSA) is a sleep disorder caused by recurrent collapse of the upper airway during sleep. The repetitive upper airway obstruction results in fractional sleep and intermittent hypoxic events overnight, which leads to adverse neurocognitive, metabolic complications and daytime sleepiness [1]. OSA is frequently observed in patients with a large body mass index (BMI), age over 40 years, or with a narrow airways and unique facial structure at birth [2].

Studies show an association of OSA with CVD morbidity and mortality with 43-73% of atrial fibrillation cases and 47-76% of heart failure cases also being OSA patients [3,4,5]. The development of CVD can be influenced by various factors, including OSA-induced endothelial dysfunction, sympathetic overactivity, inflammation, and oxidative stress [6]. The nocturnal hypoxemic burden caused by accumulated hypoxic events during sleep increases vascular inflammation, activation of the sympathetic nervous system, and blood pressure, which contributes to the appearance or exacerbation of CVD symptoms [7].

Overnight polysomnography (PSG) is commonly used for OSA diagnosis, collecting brain activity, skeletal muscle activity, heart rate, eye movement, respiratory events, and blood oxygen level. Pulse oximetry, as a part of PSG, allows a non-invasive estimation of peripheral blood oxygen saturation (SpO2) and quantifies the nocturnal hypoxemic burden. Thus, it can be recognised as a key parameter for scoring respiratory disturbance events [8].

The traditional clinical standard metrics using pulse oximetry are the oxygen desaturation index (ODI) and T90, in which ODI calculates the number of oxygen desaturation events per hour of sleep and T90 measures the time below 90% oxygen saturation [9]. Epidemiological studies show that hypopneas with oxygen desaturation are associated with CVD events and T90 is an independent predictor of mortality in patients with stable heart failure [10,11]. They suggest that the prediction of CVD outcomes could be achieved by measuring hypoxia events from pulse oximetry.

Recent studies have shown that the novel measure hypoxic burden (HB), may be a better predictor of CVD mortality in community populations and chronic heart failure-free populations [12,13]. Hypoxic burden focuses on the transient response of respiratory events during sleep and calculates the area between an estimated pre-event baseline and the SpO2 trace associated with hypoxic events. There are two key parameters in the calculation of HB: the search window and the pre-event baseline. The search window is determined by the onset and offset of the average desaturation response associated with hypoxic events of an overnight recording. The pre-event baseline is defined as the maximum value of the SpO2 signal in the 100 seconds prior to the event end [12]. HB is defined as the summed area for an overnight recording divided by the duration of sleep.

However, the reliable estimation of the area by the algorithm for HB can be challenging in some recordings. The onset and offset of the average desaturation response can be difficult to identify in noisy recordings [14]. Estimation of the pre-event baseline is also susceptible to noise in the 100

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seconds prior to each event and can be very difficult to estimate when events are less than 100 seconds apart.

In this study we seek to improve the HB algorithm by simplifying the calculation of the pre-event baseline for widespread use. We compared the current desaturation baseline algorithm (referred to as pre-event baseline) with two new methods: fixed-baseline and record-baseline. The fixed baseline used the same baseline value for all recordings. The record-based baseline determined a single baseline for each recording which was applied to all events in the recording. We compared the CVD outcomes prediction performance of each baseline method.

II. DATA

The data source used in this study is the Sleep Heart Health Study (SHHS), a multi-centre cohort study by the National Heart Lung & Blood Institute. This study provides an open-access database to determine the relationship between sleep-disordered breathing and CVD [15,16]. The database was established between 1995 and 1998 from nine existing epidemiological studies of 6641 participants whose CVD risk factors had been collected previously. All participants were aged 40 years or older, had no history of sleep apnoea treatment, tracheostomy, or current home oxygen therapy, and underwent a baseline exam with a PSG. The PSG was collected unattended in the participants' homes by trained technicians. A finger-tip pulse oximetry (Nonin, Minneapolis, MN) was used to collect the pulse oximetry data with a sampling rate of 1Hz. Sleep stage, respiratory annotations (apnoea, hypopnoea), and their associated oxygen desaturation events were scored on an epoch-by-epoch basis for all recordings [17].

The study tracked participants' CVD morbidity and mortality for up to 15 years after the first baseline examination. In the end, 4686 participants completed the SHHS study providing baseline exam data, all covariate information and CVD outcomes. In our study, the 3 baseline calculation methods for HB were applied on pulse oximetry data and the corresponding CVD mortality data used.

III. METHODS

A. Oximetry pre-processing

All the SpO2 signal values less than 50% were labelled as not a number (NaN) and ignored in later calculations.

B. HB calculation

HB was calculated as the sum of the area between the SpO2 trace and the desaturation baseline associated with all respiratory events (apnoea and hypopnoea) divided by the total time of sleep, as shown in equation 1. Three different methods of HB baseline calculation were performed and their performances in predicting CVD mortality were compared.

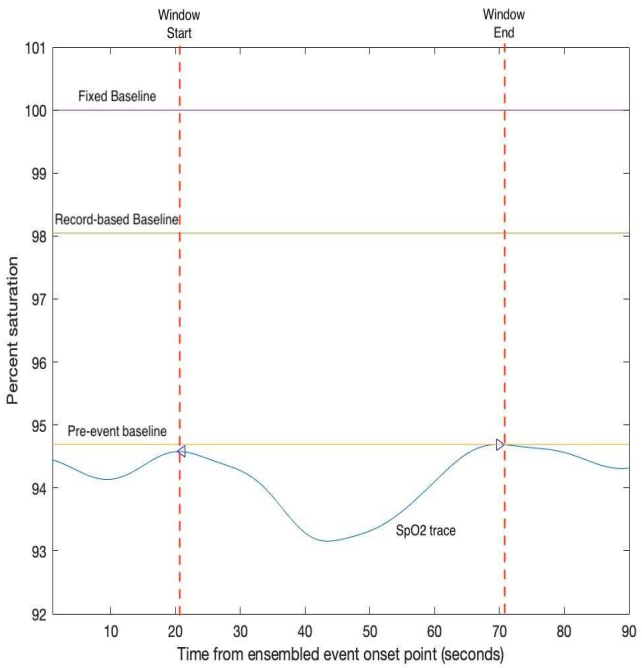

Figure 1. The main parameters required for HB calculation, including an average SpO2 trace (blue) for all respiratory events throughout the SHHS, and the three different desaturation baselines in this study. HB was calculated as the sum of the area between the SpO2 trace, the desaturation baseline, start and end point of the search window divided by the total time of sleep.

$$HB = \frac{\sum^{events} area\ between\ baseline\ and\ SpO2\ trace}{\sum time\ of\ sleep}, \qquad (1)$$

and the units of HB are %minutes per hour of sleep.

a. Sampling window

The SpO2 trace was averaged to all respiratory events (apnoea and hypopnoea) in the SHHS with each respiratory event identified by a moving sampling window. The sampling window was the same in our three different HB calculation methods. The method of Azarbarzin et al. [12] was used and the sampling window was determined by the start and end points (two peaks) associated with each respiratory event of the averaged SpO2 trace as shown in Figure 1.

b. Desaturation baseline

The three baseline methods are outlined in Figure 1. The pre-event baseline described by Azarbarzin et al. [12] was the maximum SpO2 value within 100 seconds before the end of each respiratory event. The record-based baseline varied for each recording and was calculated as the 99% ranked value of the overnight SpO2 samples in a recording.

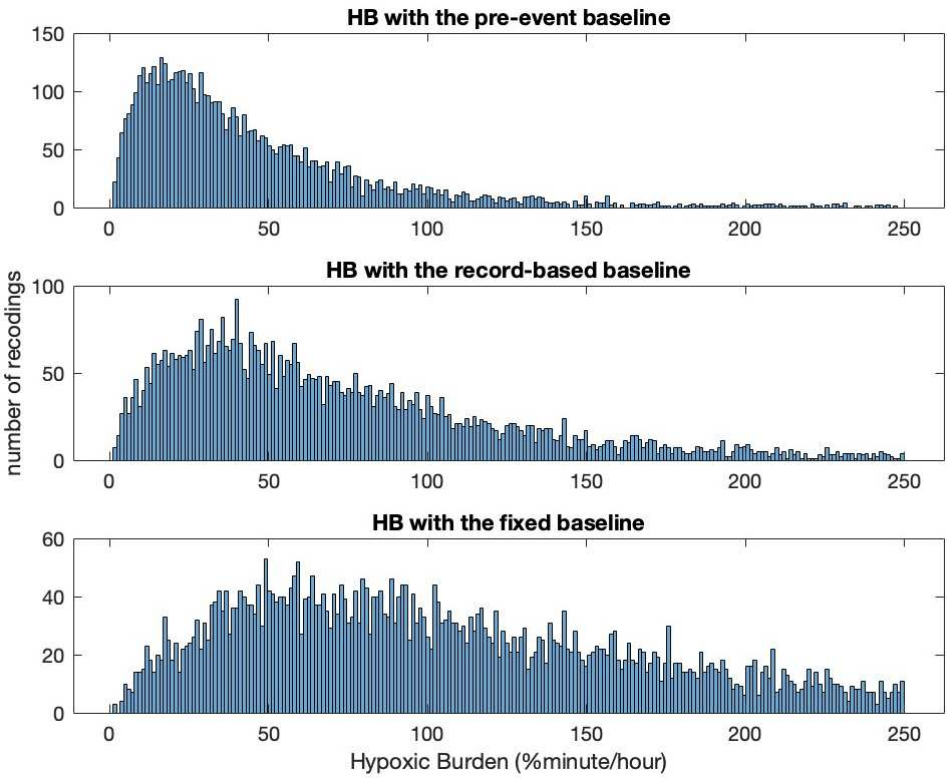

Figure 2 Histogram showing the distribution of the results of three HB calculation methods.

Table 1 HB (log-transformed, base 10) predicts the CVD mortality in SHHS using three HB calculation methods. Unadjusted and adjusted hazard ratios and 95% confidence intervals for HB in different models.

	HB with the pre-event baseline		**HB with the record-based baseline**		**HB with the fixed baseline**	
Model∗	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
0	2.60 (1.94-3.48)	<0.0001	3.45(2.50-4.77)	<0.0001	4.09(2.87-5.84)	<0.0001
1	1.33 (0.95-1.85)	0.10	1.56(1.08-2.26)	0.02	1.61(1.07-2.41)	0.02
2a	2.00 (1.07-3.73)	0.03	2.42(1.36-4.31)	<0.01	2.43(1.33-4.45)	<0.01
2b	2.21 (1.19-4.14)	0.01	2.47(1.41-4.30)	<0.01	2.43(1.37-4.32)	<0.01
3	1.76 (0.96-3.25)	0.07	2.01(1.12-3.59)	0.02	1.92(1.03-3.56)	0.04
4	1.60 (0.86-3.00)	0.14	1.83(1.03-3.27)	0.04	1.73(0.93-3.22)	0.08

∗ Model 0 is the unadjusted model. Model 1 is adjusted by age, BMI, gender, sleep duration, smoking status, and non-CVD-related medical conditions. Model 2a is adjusted by all covariates in Model 1 and AHI. Model 2b is adjusted by all covariates in Model 1 and ODI. Model 3 is adjusted by all covariates in Model 2a, MinSat, and T90. Model 4 (fully adjusted model) is adjusted by all covariates in Model 3 and concurrent cardio-metabolic diseases.

The record-based baseline was chosen at 99% to remove the any effects on the maximum value of the oximeter caused by movement on the finger during the night. The fixed baseline was set at 100% as has previously been used [14,19]. If the SpO2 trace is above the baseline, the corresponding area is not considered in the HB calculation.

Cox proportional hazard regression analysis

The results of each HB calculation method were considered as three different SpO2 predictors and compared by considering the log-transformed normalised HB value. A log transformed and the resulting distribution of the HB values was more Gaussian and had been previously used by other researcher [12,20]. Normalisation was achieved by converting each set of HBs values to z-scores by subtracting the mean value and dividing by its standard deviation. The hazard ratios were calculated by the Cox proportional hazard regression analysis [18] and were adjusted by the same covariates as [12]. Five models were considered. Model 0: unadjusted. Model 1: adjusted for demographics and non-CVD-related medical conditions. Model 2a: Model 1 and AHI.

Model 2b: Model 1 and ODI. Model 3: Model 2a and MinSat, and T90. Model 4 (fully adjusted model): Model 3 and concurrent cardio-metabolic diseases. The performance of each method in the prediction of CVD mortality was compared using the p-value of the hazard ratios.

IV. RESULTS AND DISCUSSION

Figure 2 shows the distribution of three HBs with different baseline calculation methods. The overall trend is similar for each histogram, with the largest number of participants with HB values around 50. However, there is a clear visual difference in that the HB histogram for the fixed baseline has a flatter distribution than the other methods.

Table 1 presents the unadjusted and adjusted hazard ratios and 95% confidence intervals for the three log-transformed HBs (by the different calculation methods) predicting CVD mortality. Model 0 is unadjusted, and the others are adjusted by different covariates. A hazard ratio >1 implies that an increased z score results in a higher likelihood of death and a p-value ≤ 0.05 indicates that a one standard deviation change of the HB parameter z-score, results in a statistically significant hazard ratio change. The hazard ratios for HB with the record-based baseline are statistically significant in all models, whereas the hazard ratios for HB with the pre-event baseline are not significant in models 1,3, and 4. The hazard ratios for the fixed baseline for all models except for model 4 are significant. In the fully adjusted model (Model 4), the hazard ratio for HB with the record-based baseline is 1.83 (95% CI: 1.03-3.27), which exceeds the other methods.

In summary, our study has shown that the HB calculation method using a record-based baseline may provide better prediction of CVD mortality in a community sample than the original pre-event baseline method proposed by Azarbarzin et al. [12]. The record-based baseline method has the advantage of easier calculation as it avoids the need to estimate a baseline for each event, and no predictive utility is lost by using this easier approach. The limitations of study are that we only consider a community population and that the utility of the measure in more clinically relevant populations remains untested.

V. CONCLUSION

We compared the performance of three HB calculation methods in predicting CVD mortality. HB with the record-based baseline stood out for its simplicity of calculation and good performance in the prediction of CVD mortality. This method uses a moving sampling window to identify respiratory events (apnoea and hypopnoea) and calculates the sum of the area between the record-based baseline and the SpO2 trace within each window divided by the total sleep time. We believe that this method provides a step towards a novel parameter towards early risk stratification in cardiovascular patients.

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