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Predicting Cardiovascular Outcomes Using the Respiratory Event Desaturation Transient Area Derived from Overnight Sleep Studies

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Abstract— **A new method for calculation of an overnight oximetry signal metric which is predictive of cardiovascular disease (CVD) outcomes in individuals undergoing an overnight sleep test is presented. The metric – the respiratory event desaturation transient area (REDTA) - quantifies the desaturation associated with respiratory events. Data from the Sleep Heart Health Study, which includes overnight oximetry signals and long-term CVD outcomes, was used to develop and test the parameter. Performance of the REDTA parameter was assessed using Cox proportional hazard ratios and compared to established metrics of hypoxia. Results show that hazard ratios in adjusted Cox analysis for predicting cardiovascular death using REDTA are up to 1.90 (95%CI: 1.22-2.96) which compares with the best of the established metrics. A big advantage of our metric compared to other high performing metrics is its ease of computation.**

I. Introduction

Cardiovascular disease is the leading cause of death globally. Obstructive sleep apnoea (OSA) is a serious sleep disorder that causes breathing to repeatedly stop and start during sleep through repetitive upper airway obstruction. OSA results in intermittent hypoxic events and sleep fragmentation, compromising sleep quality, and often culminating in daytime sleepiness. OSA is associated with increased risk of cardiovascular morbidity and mortality [1,2] particularly an increased risk of heart failure, stroke, and coronary artery disease [3]. Epidemiological studies show 43-73% of atrial fibrillation cases and 47-76% of heart failure cases are sleep apnoea patients [4,5].

The mechanisms underpinning the development of cardiovascular disease in OSA are multifaceted and include sympathetic overactivity, endothelial dysfunction, inflammation, and oxidative stress [6]. Nocturnal hypoxaemic burden—the cumulative exposure to hypoxaemia experienced overnight—may contribute to the pathophysiology of cardiovascular disease (CVD) by increasing the production of reactive oxygen species, vascular inflammation, autonomic imbalance, activation of the sympathetic nervous system, and elevating blood pressure [7]. The nighttime hypoxameia can be broken into two components: a persistent term that is associated with overall cardiorespiratory health and a transient term which is assocated with OSA.

OSA is diagnosed using polysomnography (PSG) which collects multiple physiological signals including brain activity, muscle activity, heart rhythm, respiratory airflow, and oxygen levels from an overnight sleep study. The nocturnal hypoxaemic burden is usually quantified using finger pulse oximetry (SpO2) and the standard clinical metrics count the number of episodic oxygen desaturations per hour of sleep (oxygen desaturation index; ODI) or measure the time spent below 90% oxygen saturation (T90) [8]. Both these metrics are easily and reproducibly calculated which has no doubt contributed to their widespread use.

Punjabi et al. [9] showed that prevalent CVD was related to the extent of hypopnoea associated oxygen desaturation during sleep. More recently, T90 was found to be an independent predictor of all-cause mortality in stable chronic heart failure patients [10] and was associated with an increased incidence of fatal stroke in community-dwelling older men [11]. This suggests measurement of intermittent hypoxia from oximetry is a potentially new and useful method of assessing CVD risk in OSA.

There are several emerging ways to quantify hypoxia from oximetry during sleep studies which focus on the transient response due to respiratory events. Two new metrics based on area under the SpO2 trace associated with respiratory events named ‘desaturation severity’ [12] and ‘hypoxic burden’ [13] appear to be better predictors than traditional PSG metrics for future cardiovascular disease mortality in cohort studies [14]. Briefly, desaturation severity sums across events the SpO2 area below the pre-event baseline to the minimum saturation point for the respiratory events and divides this sum by the duration of sleep. Hypoxic burden (HB) first determines the average desaturation response during respiratory events for an overnight SpO2 recording. It then establishes the onset and offset of the average desaturation response for the recording and forms a search window. The search window is then applied to all events and then the summed area under the SpO2 curve from the pre-event baseline is calculated and divided by the duration of sleep.

In our experience, the algorithmic requirement of both metrics to reliably identify the onset and/or offset of the desaturation response on either single events or recording averaged events can be very difficult in some SpO2 recordings. This can be due to a number of reasons including recording noise, coarse amplitude quantisation of the SpO2 signal (SpO2 signals frequently use a 1% amplitude quantisation level), and the high variability of individual responses to respiratory events. This can result in a degree of ambiguity in the window boundary points for the SpO2 area calculations and can lead to uncertainity in the hypoxemia

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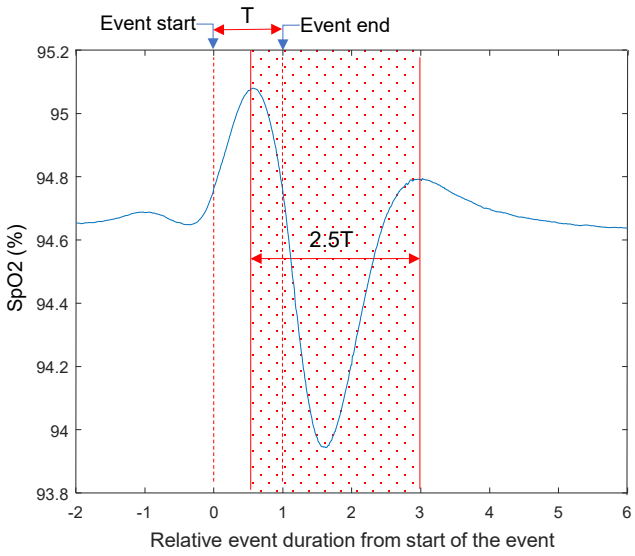

Figure 1: The average SpO2 response (blue trace) for all respiratory events across the SHHS database. The x-axis is scaled so that all events start at x=0 and finish at x=1. If the event duration is *T*, then average desaturation response (shaded) begins midway through the event and has a duration of 2.5*T*.

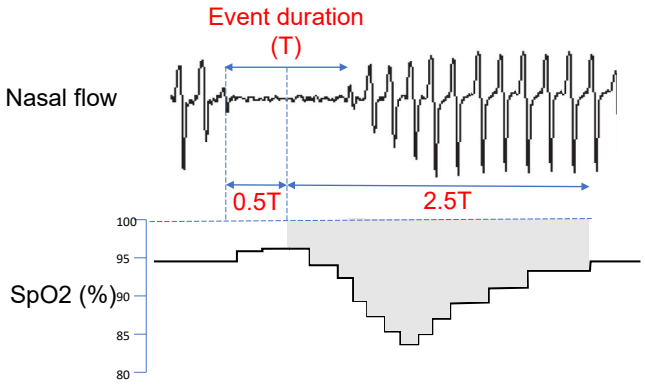

Figure 2: Calculation of the desaturation area for an individual event. The event duration *T* (in seconds) is determined and the oxygen desaturation area (shown in grey) below the 100% level in the window starting midway through the event and extending for an interval of 2.5*T*. Units of the area value are %desaturation-seconds.

metric. Both algorithms also require estimation of the pre-event SpO2 baseline for each respiratory event which can be poorly defined for noisy tracings and can lead to further uncertainity.

Inspired by these methods, we sought to develop a reproducible method that can be used for big datasets and clinical practice to measure hypoxemia based on area under the SpO2 trace with good predictivity of CVD long-term outcomes. Specifically, we sought a method that avoided the issues of previous methods i.e pre-event baseline estimation and event window boundary based on turning points. We achieved using a fixed baseline and an event window determined by timing information of the respiratory events.

After development of our new metric, we directly compared its CVD outcome predication performance against the T90, ODI3 and hypoxic burden metrics. We did not compare against the desaturation severity metric as a previous trial had shown the HB parameter provide superior performance [14]. We implemented the T90 and ODI3 metrics, but did not attempt to implement the HB metric. Rather, to enable a fair comparison, we evaluated our new metric on the same data under the same conditions as had been previously used for the HB metric [13].

II. Data

The Sleep Heart Health Study (SHHS) was used to support this study. The SHHS is a multi-centre cohort study with an open-access dataset provided by the National Heart Lung & Blood Institute. The SHHS collected data focusing on associations between CVD and sleep-disordered breathing [15-17]. The study was carried out between 1995 and 1998 in 6441 participants from five parent cohorts. The participants were aged over 40 years, without history of sleep apnoea therapy or tracheostomy or current home oxygen therapy and were recruited for a baseline study and a PSG. The PSGs were collected in an unattended home setting using a Compumedics P-Series Sleep Monitoring System. Pulse oximetry signals were collected using a finger-tip pulse oximetry using a Nonin XPOD Model 3011 (Minneapolis, MN) with a sampling rate of 1Hz.

CVD morbidity and mortality were tracked for up to 15 years after the baseline study. 4686 participants had baseline PSG signals, all covariate information and CVD outcome data. CVD mortality was used as the outcome for our study and the data included the date of death and cardiovascular disease type. There were 315 CVD related deaths.

The PSG scoring was performed using Compumedics Profusion software which included sleep staging, respiratory events annotations (apnoeas, hypopnoeas and respiratory event related arousals) and oxygen desaturation events.

III. Methods

A. *Oximetry preprocessing*

All values of the SpO2 signal less than 50% were marked as invalid and ignored in all further processing.

B. *T90 and ODI3 calculation*

The cumulative time of oxygen desaturation below 90% had previously been used by other investigators for quantifying oximetry patterns in sleep breathing disorders such as patients with Cheyne-Stokes or sleep apnoea [18,19]. For our study we used the relative cumulative time of oxygen desaturation below 90% [19]. It was calculated by finding the total time of SpO_2 below 90% during sleep and dividing by total sleep time:

$$T90 = \frac{Total\ time\ during\ sleep\ SpO2<90\%}{Total\ sleep\ time} \times 100 \qquad (1)$$

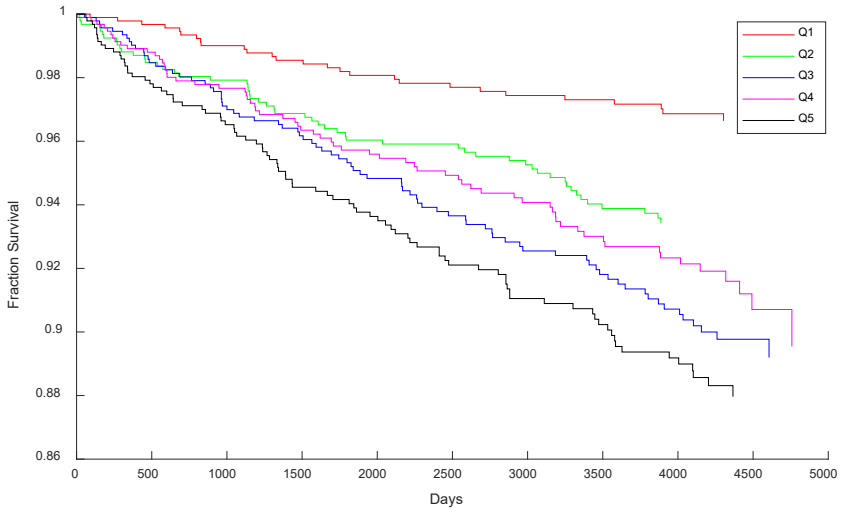

Figure 3: Survival curves for CVD mortality for quintiles of the REDTA parameter

TABLE 1. UNADJUSTED AND ADJUSTED SURVIVAL HAZARD RATIO RESULTS (Q1 IS REFERENCE) AND 95% CONFIDENCE INTERVALS FOR QUINTILES FOR THE REDTA PARAMETER AND OTHER PUBLISHED METHODS. BOLD TYPEFACE INDICATES A SIGNIFICANT RESULT WITH P<0.05.

	Unadjusted				Adjusted			
Quintiles	T90	ODI3	REDTA	Hypoxic burden*	T90	ODI3	REDTA	Hypoxic burden*
Q1	1	1	1	1	1	1	1	1
Q2	1.41 (0.92-2.16)	**2.03 (1.31-3.16)**	**2.07 (1.31-3.29)**	**1.67 (1.06-2.65)**	1.11 (0.72-1.72)	1.43 (0.92-2.23)	1.43 (0.90-2.28)	1.41 (0.88-2.24)
Q3	**1.95 (1.36-2.81)**	**2.58 (1.68-3.95)**	**3.18 (2.05-4.92)**	**2.30 (1.49-3.57)**	**1.52 (1.05-2.20)**	**1.59(1.03-2.46)**	**1.90 (1.22-2.96)**	1.25 (0.80-1.96)
Q4	**2.03 (1.41-2.91)**	**3.02 (1.98-4.59)**	**2.70 (1.72-4.23)**	**2.71 (1.76-4.16)**	1.35 (0.93-1.95)	1.45 (0.95-2.23)	1.37 (0.86-2.17)	1.51 (0.97-2.35)
Q5	**2.72 (1.92-3.84)**	**2.86 (1.87-4.36)**	**3.77 (2.44-5.80)**	**3.88 (2.56-5.88)**	**1.48 (1.03-2.13)**	1.39 (0.89-2.16)	**1.71 (1.09-2.69)**	**1.62 (1.04-2.51)**

*results from Model 0 and 1 in Table 3 in [13] which uses similar SHHS recordings and the same covariates.

ODI3 is a standard clinical measure and was provided with the SHHS database. It is defined as the number of respiratory events with an associated desaturation of 3% or more per hour of sleep. In the SHHS database, a desaturation event was triggered when the minimum SpO2 value was 3% or more in the 30 seconds beyond the end of the event than its maximum value during the event.

$$ODI3 = \frac{Number\ of\ desaturation\ events*}{Total\ sleep\ time\ in\ hours} \times 100 \qquad (2)$$

$*\ desaturation\ event :=$
$(max(SpO2\ during\ event) - min(SpO2\ during\ event + 30\ seconds)$
$>= 3\%)$

C. Hypoxic burden (HB)

We did not implement the HB method and therefore do not provide calculation details. See [13] for details.

D. Survival curves and Cox proportional hazard regression analysis

Each SpO2 parameter was grouped into quintiles. Using the CVD mortality outcome data (outcome and date of outcome), the survival curves [20] for CVD mortality were estimated for each quintile. Additionally, hazard ratios from Cox survival hazard analysis [21] were calculated to obtain a quantitative comparison of the association between predictor variables and the survival time of the participants. The Cox models were adjusted using the same variables as Model 1 in [13] i.e. age, body mass index, sex, race, sleep duration, smoking, and chronic obstructive pulmonary disease.

IV. EXPERIMENTS

A. Development of the Respiratory Event Desaturation Transient Area (REDTA) parameter

1) Sampling Window

The average SpO2 response to all respiratory events (apnoeas, and hypopnoeas) was calculated across the SHHS database. Each respiratory event was identified using the Compumedics events files and the start *S*, finish *F* and duration *T* identified. As a respiratory event influences the oxygen saturation response in the period immediately after the event, we first removed the events that occurred within 2 minutes of a previous event to avoid compounding SpO2 effects. For all remaining events, the section of SpO2 signal from *F-2T* to *F+6T* was extracted. This section was then uniformly resampled into 800 samples and stored. After resampling, all event responses were averaged to produce the average SpO2 response shown in figure 1. In all, 185,443 events were used to calculate figure 1.

As indicated in figure 1, there is an average transient response to respiratory events that begins at one event length before the event onset and extends for approximately six event length periods. The average SpO2 response initially decreased before the event, then increased during the event and peaked midway during the average event response. Following this the main desaturation response occurs over two and half event lengths (figure 1 red shaded section). This

was followed by a period of two event lengths with a small decrease in saturation.

2) Calculation of REDTA value

Based on the average desaturation response, we calculated the REDTA metric as follows.

- For each respiratory event, we calculated the area between 100% and the SpO2 curve from midway through the event and extending for 2.5 event lengths (see figure 2). The area is scaled so the area units are %seconds. When an event occurred within 2.5 event length of the previous event, we only included the SpO2 samples that were beyond the previous window in the area calculation thus avoiding double counting of areas.
- The REDTA value is then calculated by summing the areas for events and dividing by 3600.

$$REDTA = \frac{\sum_{\text{events}} desaturations\ areas\ below\ baseline}{3600} \quad (3)$$

The units of the REDTA metric are %hours. More events, longer events and larger desaturations all increase the value of REDTA. The REDTA value measures the contribution to the total accumulated desaturation that is associated with the respiratory event oxygen desaturation transient.

V. Results and Discussion

The T90, ODI3 and REDTA metrics were calculated for our SHHS recordings, divided into quintiles and then survival curves and Cox survival hazard analysis determined. These results were then directly compared to the HB results in models 0 and 1 in table 3 in [13]. They are comparable as [13] uses the same analysis tools on quintiles of the HB metric calculated from a similar subset of the SHHS (we used 4686 recordings, [13] uses 4672 recordings) and uses the same covariates in the adjusted Cox analysis.

Table 1 shows the Cox's survival hazard analysis for T90, ODI3, REDTA and HB [13] and compares the hazard ratio (HR) of Q2-5 to the Q1. An HR>1 indicates a higher likelihood of death relative the Q1. Except for Q2 of the T90 metric, all unadjusted results are significant at P=0.05 threshold. After adjusting for known confounding covariates, significant results were observed for Q3 and Q5 of REDTA and T90, Q3 of ODI and Q5 of HB. The adjusted HR for Q3 and Q5 of the REDTA parameter exceeded all other parameters.

Figure 3 shows the survival curves for the quintiles of the REDTA parameter. There is a clear visual difference between survival outcomes of the Q1 (REDTA values 0-2.15%hr) and Q5 (REDTA values 13.1-164%hr). By day 4000, 3.0% of participants in Q1 had died, while 11% in Q5 had died. The major limitation of this study is that it is a retrospective study and that the sampling window is derived from the same data.

VI. Conclusion

We have developed a hypoxemia metric, the REDTA, that measures the oxygen desaturation associated with respiratory events. The metric uses a fixed sampling window derived from the average oximetry response to respiratory events from more than 4500 overnight PSGs. The metric was shown to be a predictor of CVD outcomes independent of confounding covariates and to provide prediction performance comparable to the best of other metrics. A big advantage of our metric compared to other high performing metrics is its computational simplicity and reproducibility. We believe the metric is an important enabling step towards clinical methods that provide risk stratification and early intervention on CVD outcomes from the PSG.

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