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# Is dynamic desaturation better than a static index to quantify the mortality risk in heart failure patients with Cheyne-Stokes respiration?

Philine Granitza,<sup>1</sup> Jan F. Kraemer,<sup>1</sup> Christoph Schoebel,<sup>2</sup> Thomas Penzel,<sup>2,3</sup> Jürgen Kurths,<sup>1,4,5</sup> and Niels Wessel<sup>1,a)</sup>

<sup>1</sup>Department of Physics, Cardiovascular Physics, Humboldt-Universität zu Berlin, 10099 Berlin, Germany

<sup>2</sup>Interdisziplinäres Schlafmedizinisches Zentrum, Charité-Universitätsmedizin Berlin, 10117 Berlin, Germany

<sup>3</sup>International Clinical Research Center, St. Anne's University Hospital Brno, 656 91 Brno, Czech Republic

<sup>4</sup>Potsdam Institute for Climate Impact Research (PIK), 14412 Potsdam, Germany

<sup>5</sup>Institute for Complex Systems and Mathematical Biology, University of Aberdeen, Aberdeen AB24 3UE, United Kingdom

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Cheyne-Stokes respiration (CSR) is a periodic, highly dynamic, respiratory pattern and a known comorbidity in congestive heart failure (CHF) patients. It is generally seen as an indicator for a negative prognosis, even if no distinction in degree is known or understood. This paper aims to improve on existing attempts by creating a quantification of the behavior of the dynamic desaturation process of oxygen in the blood. We performed this work on a cohort of 11 subjects with CHF, reduced left ventricular ejection fraction, and CSR. The dynamic desaturation process was evaluated according to changes to peripheral capillary oxygenation  $SpO_2$  resulting from highly nonlinear relationships in the ventilatory system perturbed by periodic breathing. Hypoxaemic burden expressed as a static index  $T90$  was compared to a novel relative desaturation index  $RDI$ , developed in this paper. While  $T90$  represents a single value calculated using a static cut-off value of 90%  $SpO_2$ , the  $RDI$  is more sensitive to dynamic influences as it uses the specific maximum change in saturation for each CSR episode. The threshold of  $T90 = 22$  min per night as suggested by Oldenburg *et al.* could not be confirmed to predict survival, but all central apneas resulting in a relative desaturation of  $SpO_2$  above a cut-off value of 8% were a 100% positive predictor of mortality. The  $RDI$  proved sufficiently stable in intraindividual measurements across CSR epochs. Across the cohort, it showed a bimodal distribution for the deceased group, indicative of a possible aetiological difference. Hence, it is our conclusion that a dynamic approach to analyse desaturation of oxygen during Cheyne-Stokes respiration is to be strongly favoured over a static approach to analysis. *Published by AIP Publishing.*  
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Sleep disordered breathing (SDB) is a common phenomenon in patients with heart failure, with an estimated prevalence of 47 – 76%.<sup>1</sup> One form of SDB is Cheyne-Stokes respiration, meaning periodically occurring epochs of unusually deep and rapid breathing (hyperpnea) alternating with a complete lack of respiratory drive (central apneas). Like many other dynamical diseases,<sup>2</sup> especially those with cardiac involvement,<sup>3–5</sup> the nonlinear dynamics of CSR have been the object of research for several decades at this point.<sup>6,7</sup> Although CSR is associated with an increased mortality in heart failure patients,<sup>8</sup> there is currently no proven beneficial effect on survival through therapy.<sup>9</sup> In clinical practice, the severity of CSR is often quantified using the static apnea-hypopnea index (AHI);<sup>1,10</sup> more recently, another static measure, hypoxaemic burden  $T90$ , was suggested to stratify mortality risk.<sup>10</sup>

In this paper, the dynamic approach of the novel relative desaturation index  $RDI$  is introduced, which captures and quantifies the dynamics of desaturation of oxygen in the blood. It is remarkably stable over sufficiently long CSR episodes across the whole night and shows a high

degree of separation regarding mortality in the cohort of this study.

We want to use this focus issue in honour of Hans Braun to further disseminate this medically highly relevant and current topic in this research community in the hope of increasing the number of nonlinear approaches to modelling applied to a better understanding of the aetiopathology of CSR and possible treatment options.

## I. INTRODUCTION

Cheyne-Stokes respiration is a condition first described in the 19th century by Irish doctors John Cheyne<sup>11</sup> and William Stokes.<sup>12</sup> It refers to a distinctive crescendo-decrescendo respiratory pattern (as seen in Fig. 1) of periodic epochs of unusually deep and rapid breathing (hyperpnea) alternating with a complete lack of respiratory drive (central apneas) most often occurring during sleep. This is caused by a vicious cycle in the regulatory mechanism of respiration, facilitated by an abnormal and/or delayed reaction to the chemoreflex, altered cerebrovascular  $CO_2$  reactivity, and elevated sympathetic nerve activity. It has been

<sup>a)</sup>Niels.Wessel@physik.hu-berlin.de

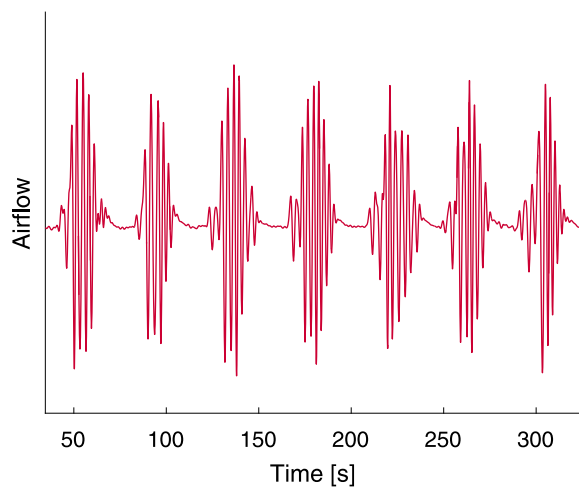


FIG. 1. Periodic breathing pattern of a patient with Cheyne-Stokes respiration. Central apneas are followed by increasingly deeper breaths which then transition to central apneas again.

shown to have an elevated prevalence in patients with congestive heart failure or subjects at high altitudes.<sup>13–15</sup> Hyperventilation drastically decreases  $Pa_{CO_2}$ , the partial pressure of  $CO_2$  in the arterial blood, a delayed chemoreflex leads to central apnea, which increases  $Pa_{CO_2}$  above the apneic threshold, leading to hyperventilation, completing the cycle.<sup>15</sup> The seriousness of this comorbidity in patients with CHF, which

also results in a disrupted sleep structure and its own consequences, leads to a generally poor rate of survival for those patients affected.<sup>8</sup> Recent research has shown no beneficial effect on survival through therapy,<sup>9,16</sup> and there is currently an ongoing discussion in the medical community, whether CSR is a compensatory, i.e., beneficial, mechanism in CHF patients or whether it should be suppressed.<sup>17,18</sup> The aim of this paper is to further the development of personalised medicine<sup>2</sup> by introducing the relative desaturation index. This index is a new measure to differentiate between groups of patients that will respond to specific therapies and to identify those whose treatment requires completely new approaches. The evaluation of treatment efficiency<sup>19</sup> is a first but necessary step to achieve this goal.

## II. METHODS

### A. Data

We selected a cohort of two groups of male patients with Cheyne-Stokes respiration, who were either deceased ( $n_d = 10$ ) or alive ( $n_s = 10$ ) at the time of data export. They were matched for *BMI* and age. All patients of this cohort suffered from congestive heart failure with reduced left ventricular ejection fraction ( $LVEF \leq 45\%$ ). Informed consent was obtained from each subject. During the course of the study, the data from multiple subjects turned out to be unsuitable for analysis for technical reasons and had to be excluded. There remained data from  $n_d = 5$  deceased and  $n_s = 6$  surviving

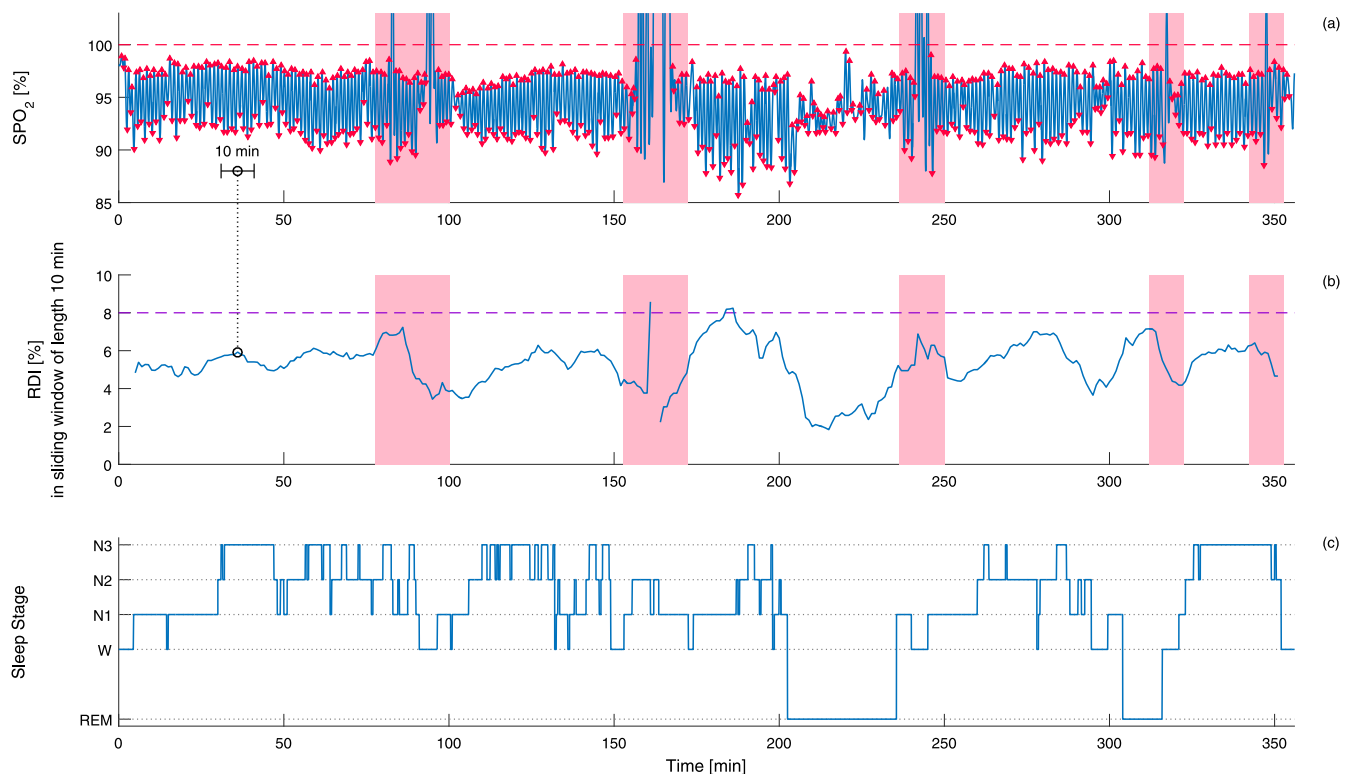


FIG. 2. Subject *p2* showed Cheyne-Stokes respiration during the entire recording period. The resulting periodic changes in  $SpO_2$  (a) were captured with the novel relative desaturation index *RDI* in a sliding window of width  $w = 10$  min in steps of  $s = 1$  min (b). Values of  $SpO_2 > 100\%$  are unphysiological and are thus considered artefacts. The *RDI* values possibly affected by those artefacts, i.e.,  $w/2 = 5$  min before and after, are shaded in red and could be excluded. The *RDI* values are restricted to a limited range of  $(5.3 \pm 1.2)\%$ . Except for a reduction of *RDI* during the first episode of REM sleep, there does not appear to be a correlation to sleep stages (c).

patients. The diagnostic polysomnographies were analysed for total time in bed, sleep stage, air flow, and peripheral capillary oxygen saturation ( $Sp_{O_2}$ ).

### B. Hypoxaemic burden T90

Recently, Oldenburg *et al.*<sup>10</sup> identified the hypoxaemic burden  $T90$

$$T90 = \text{time}(Sp_{O_2} < 90\%) \quad (1)$$

as an independent predictor of time to death from any cause in patients with CHF and reduced  $LVEF$ . Patients presenting  $T90 > 22$  min per night were at increased risk of death as compared to those with a lower  $T90$  duration.

Previously, Hildenbrand *et al.*<sup>20</sup> compared the percent of time spent in bed with  $Sp_{O_2} < 90\%$  in pulmonary arterial and chronic thromboembolic pulmonary hypertension patients and showed it to reflect disease severity.

In this paper, the absolute value  $T90$  in [min per night], as by Oldenburg *et al.*, shall be referred to as  $T_{a90}$ , while the relative approach by Hildenbrand *et al.* is called  $T_{p90}$  and measured in [% of night].

### C. Relative desaturation index $RDI$

The effect of each CSR cycle during a 10 minute segment of continuous periodic breathing on the oxygen level of the blood is evaluated. Each central apnea  $i$  in this segment is associated with the resulting desaturation of  $Sp_{O_2}$ :

$$(\Delta Sp_{O_2})_i = \max[(Sp_{O_2})_i] - \min[(Sp_{O_2})_i]. \quad (2)$$

The novel relative desaturation index  $RDI$  is defined as the mean of the desaturation  $\Delta Sp_{O_2}$ :

$$RDI = \text{mean}_{\forall i}(\Delta Sp_{O_2}) \quad (3)$$

and can be extended to include the standard deviation. To characterise this parameter and its information value, it was calculated in a sliding window of width  $w = 10$  min in steps of  $s = 1$  min over the whole duration of measurement for patient  $p2$ . This patient was part of the surviving subcohort and showed the periodic breathing pattern during the whole length of the recording.

The  $RDI$  was then calculated for the first continuous 10 min of CSR in nREM sleep for each patient of the cohort. Furthermore, to allow a comparison to the approach by Oldenburg *et al.*<sup>10</sup>, a hypoxaemic burden  $U_{p90}$  was defined that applied the  $T_{p90}$  methodology to the same 10 continuous minutes of CSR used for  $RDI$ -calculation across the cohort. The chosen window length of 10 min is supported by the fact that historically, CSR used to be diagnosed in coherence with a consensus definition of 10 min of periodic breathing.<sup>21</sup>

## III. RESULTS

### A. Intraindividual stability of the $RDI$ parameter

To allow the interindividual comparison of a selected segment of CSR, we evaluated the longterm behavior of the  $RDI$  parameter over differing sleep stages. We were fortunate that subject  $p2$  showed CSR during the entire recording period [see  $Sp_{O_2}$  channel in Fig. 2 (a)].

For each sliding window of width  $w = 10$  min, the parameter's values are restricted to a limited range of  $(5.3 \pm 1.2)\%$ , which would contract even further if limited to periods of nREM sleep. It can thus be argued to be of no concern, which 10 min interval is analysed provided that it is part of a sufficiently long CSR episode during nREM sleep.

### B. Intergroup comparison of dynamic $\Delta Sp_{O_2}$ response to CSR

The histograms in Fig. 3 contain all desaturation values  $\Delta Sp_{O_2}$  for surviving (a) as well as deceased (b) CSR patients during 10 min of continuous CSR. In survivors, the CSR episodes result in a relative desaturation index of  $RDI_s = 3.9 (\pm 1.9)\%$ , with all desaturations  $\forall_{i \text{ from } s}: (\Delta Sp_{O_2})_i < 8\%$ . Non-survivors however show a bimodal distribution (separated at 5%) with  $RDI$  values of  $2.2 (\pm 0.9)\%$  and  $8.5 (\pm 1.6)\%$ , respectively.

Looking at each central apnea of patients  $p8$  and  $p11$ , they all resulted in desaturations of  $\forall_{i \text{ from } \{p8, p11\}}: (\Delta Sp_{O_2})_i < 5\%$ ; meanwhile all apneas (except for one outlier each) of patients  $p7$ ,  $p9$  and  $p10$  resulted in desaturations  $> 5\%$ . Thus, deceased patients are clearly separated into two subgroups.

To show that the distributions of  $\Delta Sp_{O_2}$  of survivors and non-survivors are not in fact subgroups of the same distribution, the Lilliefors test for normal distribution was performed for each group. The resulting  $p$ -values

$$p_s = 0.374$$

$$p_d = 0.001,$$

indicate that while  $(\Delta Sp_{O_2})_d$  is probably not normally distributed,  $(\Delta Sp_{O_2})_s$  might be.

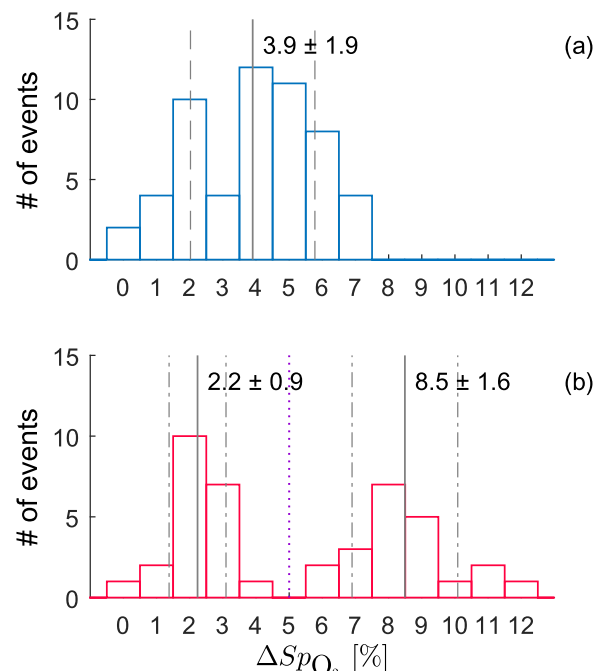


FIG. 3. Histograms of desaturation in peripheral capillary oxygen saturation  $\Delta Sp_{O_2}$  following CSR-apneas for both surviving (a) and non-surviving (b) patients. The distribution for non-survivors is bimodal, separated at 5%, with one subgroup's central apneas resulting in desaturations higher than survivors', indicative of different aetiologies.

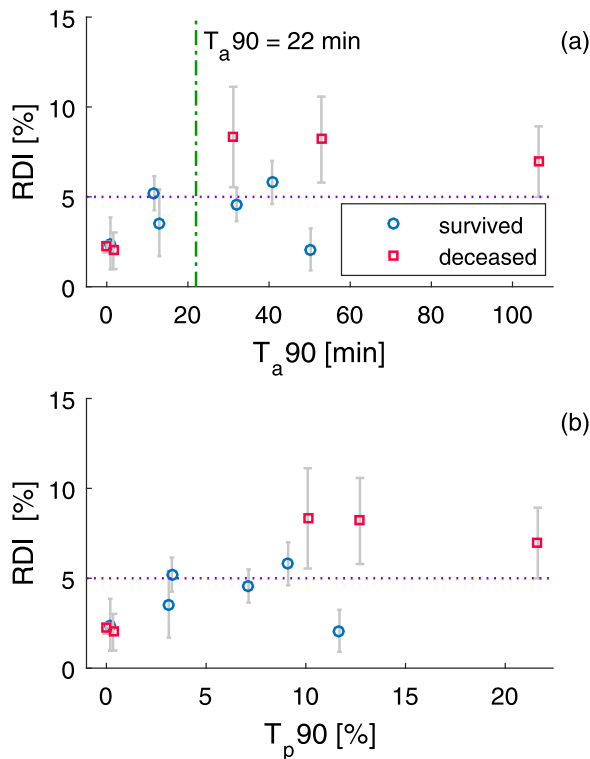


FIG. 4. Relationship of the relative desaturation index  $RDI$  with hypoxaemic burdens  $T_{a90}$  and  $T_{p90}$  in plots (a) and (b), respectively, for surviving (blue) and deceased (red) CSR-patients. An  $RDI$  of 5% separates deceased patients into two subgroups; while this same separation is observed by using the threshold of Oldenburg *et al.*<sup>10</sup> at  $T_{a90} > 22$  min per night, it does not reliably distinguish the surviving and non-surviving groups as claimed by its originators.

### C. Comparison of a dynamic descriptor to an existing static index of $\Delta Sp_{O_2}$ response to CSR

Table I lists the resulting values for each CSR patient of  $T_{a90}$ ,  $T_{p90}$ ,  $U_{p90}$  as well as  $RDI$  during the same 10 min of continuous CSR. The varying durations of measurement result in a clearly noticeable difference in scale of the calculated values. The relative hypoxaemic burden  $U_{p90}$  during 10 minutes of CSR does not hold any additional information, besides clearly defining the same subset of non-survivors that can also be found using the  $RDI$ .

A visualisation of the relationship of the  $RDI$  with  $T_{a90}$  and  $T_{p90}$  in Figs. 4(a) and 4(b), respectively, shows this separability of the deceased patients into two subgroups at

$RDI = 5\%$ . A threshold of  $T_{90} > 22$  min per night as set by Oldenburg *et al.*<sup>10</sup> as predictor for time until death in patients with CHF and reduced  $LVEF$  equally separates non-surviving CSR patients into the same subgroups. It does not, however, reliably distinguish between surviving and deceased CSR patients in our cohort.

## IV. DISCUSSION

The absolute approach of Oldenburg *et al.*<sup>10</sup> measuring the hypoxaemic burden  $T_{a90}$  in [min per night] is apparently not well defined. It does not account for duration of measurement, thus the threshold of 22 min as predictor for time until death is potentially misrepresentative and should be re-defined in the relative unit of measurement [% per night]. Furthermore, no test of significance was provided, so that the resulting risk stratification cannot be considered evidence based. Having been defined for patients with CHF and reduced  $LVEF$ , the 22 min threshold does not reliably differentiate between the surviving and non-surviving patients under study, who differ from the original group by being diagnosed with the highly prevalent comorbid condition of CSR.

Capturing the dynamic changes in relative  $Sp_{O_2}$  desaturation for all central apneas of patient  $p2$  inside a sliding window has revealed the novel relative desaturation index  $RDI$  to be sufficiently stable to limit the evaluation to one 10 min period of continuous CSR during nREM sleep for each cohort patient. This analysis revealed a cut-off value of  $\Delta Sp_{O_2} \geq 8\%$  to be a 100% positive predictor of mortality in this limited sample. The novel relative desaturation index  $RDI$  has yielded a bimodal distribution of deceased CSR patients, indicating possible aetiological differences.

The arterial partial oxygen pressure of the blood  $Pa_{O_2}$  is the result of multiple highly nonlinear influences. Under normal circumstances, it varies by about 8 mmHg with respiration<sup>22</sup> and decreases with age. Young healthy adults have an average value of approximately 95 mmHg, while at age 60 years this is reduced to 85 mmHg.<sup>23</sup> In accordance with the oxygen-haemoglobin dissociation curve in Fig. 5, older patients thus have an inherently higher chance of an oxygen saturation  $SO_2$  below 90% without actually suffering from any form of SDB.

The continuous waxing and waning pattern of Cheyne-Stokes respiration, alternating between apneas and hyperventilation, causes continuous changes in alveolar ventilation.<sup>23</sup>

TABLE I. The absolute and relative hypoxaemic burdens  $T_{a90}$  and  $T_{p90}$  measured in [min per night] and [% per night], respectively, differ due to varying durations of measurement. During 10 continuous minutes of Cheyne-Stokes respiration, the relative desaturation index  $RDI$  appears to divide non-surviving patients into two subgroups, one of them also clearly separated from survivors. In the same timespan, the relative hypoxaemic burden  $U_{p90}$  holds no additional information.

Patient	Survivors						Non-survivors				
	$p1$	$p2$	$p3$	$p4$	$p5$	$p6$	$p7$	$p8$	$p9$	$p10^a$	$p11$
$T_{a90}$ (min)	0.91	11.72	32.00	40.75	50.25	12.95	52.89	0	31.20	106.44	1.62
$T_{p90}$ (%)	0.19	3.28	7.13	9.12	11.69	3.13	12.71	0	10.10	21.63	0.33
$U_{p90}$ (%)	0	0	0	0	0	0	23.27	0	18.66	33.75	0
$RDI$ (%)	$2.4 \pm 1.4$	$5.2 \pm 0.9$	$4.6 \pm 0.9$	$5.8 \pm 1.2$	$2.1 \pm 1.2$	$3.6 \pm 1.9$	$8.2 \pm 2.4$	$2.2 \pm 0.3$	$8.3 \pm 2.8$	$7.0 \pm 2.0$	$2.0 \pm 1.0$

<sup>a</sup>All data signals of patient  $p10$  were cut after about half of the night and no longer evaluable.



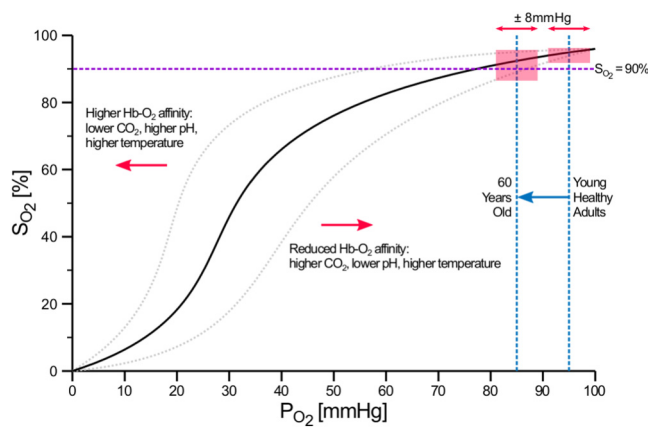


FIG. 5. The Bohr effect makes the oxygen-haemoglobin dissociation curve shift with temperature,  $P_{aCO_2}$ , and  $pH$ . At the same time, the arterial partial oxygen pressure  $P_{aO_2}$  varies by  $\approx 8$  mmHg with respiration, the mean decreases with age. Thus, apneas result in more reduction of  $Hb - O_2$  affinity in older patients than younger ones.

This leads to variations in arterial partial pressure of oxygen,  $P_{aO_2}$  and carbon dioxide,  $P_{aCO_2}$ , which in turn changes the  $pH$  of the blood and induces the Bohr effect,<sup>24</sup> shifting the oxygen-haemoglobin dissociation curve along the  $P_{aO_2}$ -axis. As a result, the measured  $S_{O_2}$  in CSR patients shows an even higher variation in response to equal stressors compared to their demographic equals.

This differing range of variation as response to the apneic stressor corroborates the need to study the relative changes in  $Sp_{O_2}$  as enabled by our novel *RDI* approach. This parameter, through its focus on the effects of acute respiratory changes, is more suitable for detailed analysis of the dynamics and pathophysiological consequences of CSR compared to the existing measures of Oldenburg *et al.* ( $T_{a90}$ ) and Hildenbrand *et al.* ( $T_{p90}$ ).

## V. OUTLOOK

It should be noted that, due to lack of availability of sufficiently preprocessed data, the evaluation of *RDI*, our novel desaturation index, has so far been limited to a small cohort and manual selection of a 10 minute epoch of interest. Future research is planned to integrate the calculation of the *RDI* parameter into an automatic scoring system allowing the study of this index on larger cohorts, now existing due to large randomised studies that have been conducted in recent years.<sup>9,25</sup> We hope that tools such as the *RDI* will help explain differences in therapeutic efficiency and might create a possibility for a more personalised approach to sleep medicine. Another aspect is to integrate the *RDI* with the apnea-hypopnea index *AHI* and measures based on cardiorespiratory coordination<sup>26,27</sup> to allow for the consideration of apneic events and their nightly prevalence as well as their impact on the cardiovascular system. It is hoped to be more informative regarding prognosis and need for therapy as compared to *AHI* individually in the diagnostics of SDB.<sup>28</sup> One similar conclusion was reached in Kulkas *et al.*,<sup>29</sup> which argued that the desaturation area  $s\%$  is a promising weighting factor for the *AHI* allowing for the inclusion of severity,

thus allowing a continuous scale from obstructive hypopnea to apnea.

Since the American Academy of Sleep Medicine, in the case of CSR, already adopted a more dynamic set of criteria for diagnosis,<sup>21,30</sup> there appears to be a growing awareness of the insufficiency of purely relying static measures. The *RDI*, which was presented in this work and captures the dynamic behavior of the respiratory regulatory system in CSR better than established static measures, is another tool for this changing diagnostic environment.

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