Aus der Hals-, Nasen-, Ohren-Klinik und Poliklinik - Plastische Operationen
der Universitätsmedizin der Johannes Gutenberg-Universität Mainz

Einfluss des Schweregrades der obstruktiven Schlafapnoe auf die Häufigkeit der zentralen Apnoen im REM-Schlaf, sowie auf die Mikrostruktur der cortikalen respiratorischen Arousals

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Abkürzungsverzeichnis

OSA	obstruktive Schlafapnoe
ICSD	International Classification of Sleep Disorders
AASM	American Academy of Sleep Medicine
UPS	Unterkieferprotrusionsschiene
UPPP	Uvulopalatopharyngoplastik
CAE	central apnea event
ML	machine learning
SVM	support vector machine
AI	artificial intelligence
KI	künstliche Intelligenz
REM	Rapid Eye Movement
NREM	Non rapid eye movement
AUC	area under the curve
EEG	Elektroenzephalographie

1 Einleitung

1.1 Obstruktive Schlafapnoe (OSA)

Die obstruktive Schlafapnoe (OSA) gehört laut der International Classification of Sleep Disorders (ICSD) zu den schlafbezogenen Atmungsstörungen, welche einer der sechs Hauptgruppen ist, die durch die American Academy of Sleep Medicine (AASM) klassifiziert wurde (1). Dabei ist OSA eine sehr häufige schlafbezogene Atmungsstörung, bei der es zu wiederholenden Phasen von kompletter Apnoe oder Hypopnoe durch die Obstruktion der oberen Atemwege kommt. Die Prävalenz von OSA mit dazugehöriger Tagesschläfrigkeit im Alter von 30-60 Jahren bei Männern wird auf 3-7% und bei Frauen auf 2-5% geschätzt (2). Kapur et al. konnte in einer Studienübersicht zusätzlich aufzeigen, dass in verschiedenen Populationen die Prävalenz der Erkrankung annähernd gleich ausfällt, wie in Abbildung 1 dargestellt (3).

					Prevalence (%)	
Country	First Author	*N*	Ethnicity	Diagnostic Method	Men	Women
United States	Young[32]	602	White	Polysomnography	4.0	2.0
United States	Bixler[33]	1,741	White	Polysomnography	3.9	1.2
Australia	Bearpark[34]	485	White	MESAM IV*	3.1	ND
India	Udwadia[35]	250	Indian	Polysomnography	7.5	4.5
China	Ip[36]	258	Chinese	Polysomnography	4.1	ND
China	Ip[37]	ND	Chinese	Polysomnography	ND	2.1
Korea	Kim[38]	457	Korean	Polysomnography	4.5	2.3

* MESAM IV (Madaus, Marburg, Germany) is a portable sleep monitoring system.
ND = no data available
(Adapted from Reference 39.)

Abbildung 1: „Table 1. Studies on the Prevalence of Obstructive Sleep Apnea" aus Kapur et al. Obstructive sleep apnea: diagnosis, epidemiology, and economics

Zur diagnostischen Definition laut AASM sollen die Episoden von Apnoe oder Hypopnoe mindestens 10 Sekunden anhalten. Hypopnoen müssen dabei eine Dezeleration von ≥ 30% des nasalen Drucksensors und einen Sättigungsabfall von ≥ 4% zum Ausgangswert haben. Dabei können entweder ≥ 5 Episoden pro Stunde gepaart mit einem der folgenden Symptome durch eine Polysomnographie oder außerhalb eines Schlaflabors (z.B. durch eine Polygraphie) getestet werden:

1. Der Patient gibt Müdigkeit, nicht erholsamen Schlaf, Fatique oder Symptome der Insomnie an
2. Der Patient erwacht mit Atemnot, Keuchen oder Würgen
3. Der Bettpartner oder ein anderer Beobachter berichtet über gewohnheitsmäßiges Schnarchen, Atemaussetzer oder beides während des Schlafes des Patienten
4. Bei dem Patienten wurden Bluthochdruck, eine Gemütsstörung, kognitive Dysfunktion, koronare Herzkrankheit, Schlaganfall, kongestive Herzinsuffizienz, Vorhofflimmern oder Diabetes mellitus Typ 2,

oder es werden ≥ 15 Episoden pro Stunde durch Polysomnographie oder außerhalb eines Schlaflabors festgestellt (1). Die genauen Bewertungskriterien der respiratorischen Ereignisse innerhalb der Polysomnographie, werden durch das „AASM-Manual for the Scoring of Sleep and Associated Events" festgelegt (4). Aus dem Apnoe/Hypopnoe-Index (AHI), der die Anzahl der Apnoen und Hypopnoen je Stunde Schlafzeit angibt wird die Einteilung des Schweregrades in mild (AHI 5-15/Std.), moderat (AHI 15-30/Std.) und schwer (AHI >30/Std.) getroffen (5). Die Apnoe und Hypopnoe mit Sättigungsabfall werden meistens beendet von einem unbewussten Erwachen aus dem Schlaf. Die Ereignisse können in allen Schlafphasen (N1, N2, N3 und REM) vorkommen, jedoch sind sie in den Phasen N1, N2 und REM häufiger zu beobachten als in der Tiefschlafphase N3. Das dauerhaft präsente Hauptsymptom für viele, jedoch nicht alle Patienten, ist eine exzessive Tagesschläfrigkeit. Die Tagesschläfrigkeit ist eine

starke Beeinträchtigung während allen Tagesphasen, sei es in Ruhe, körperlichen Aktivitäten, der Arbeit oder während des Fahrens von Kraftfahrzeugen. Auch können Insomnie, schlechte Schlafqualität und Fatigue zum Symptomkomplex der OSA gehören. Während des Schlafens kann es zu starkem Schnarchen kommen. Insgesamt führt die Symptomatik zu einer stark eingeschränkten Lebensqualität der Patienten. Subjektiv zu bewertende Tests zur Bestimmung der Tagesschläfrigkeit, wie die Epworth Sleepiness Scale oder objektivierbare Tests, wie der Multiple Sleep Latency Test (MSLT) können zur Diagnostik unterstützend hinzugezogen werden. Problematisch bleibt jedoch, dass viele Patienten, bis auf eine leichte Fatigue oder Müdigkeit, welche häufig nicht als pathologisches Symptom gewertet wird, asymptomatisch sind. Daher kommt es meist zu einer späten Diagnose, welche erst aufgrund von langfristigen Folgeerscheinungen oder assoziierten Erkrankungen gestellt wird. Dies kann zum Beispiel eine erhöhte Unfallneigung, arterielle Hypertonie, Herzinsuffizienz, Cor pulmonale, Herzrhythmusstörungen, ein Herzinfarkt, Arteriosklerose oder ein Schlaganfall sein (1, 3, 5-10). Das Risiko an OSA zu erkranken ist an modifizierbare und nicht modifizierbare Faktoren gebunden (11). Zu den nicht modifizierbaren Faktoren, welche das Risiko steigern können, gehört einerseits das Geschlecht, Alter und die kraniofaziale Anatomie (12-15). Andererseits aber auch die ethnische Herkunft (16). Zu den modifizierbaren Faktoren, gehört als sicherlich wichtigster Faktor, das Übergewicht, aber auch sedierende Medikation, endokrinologische Erkrankungen und das Rauchen (16-18). Die Pathogenese der schlafbezogenen Atmungsstörung ist multifaktoriell und beruht auf zentralnervösen und/oder neuromuskulären Prozessen, die zu Veränderungen der zentralen Atemregulation und/oder des Muskeltonus der oberen Atemwege während des Schlafes führen. Die genaue Pathogenese ist jedoch noch im Mittelpunkt der Forschung und ist noch nicht vollständig geklärt.

Therapeutisch stehen den Patienten eine Vielzahl an Behandlungsmöglichkeiten zur Verfügung, welche isoliert oder in Kombination genutzt werden können. Ziel der Behandlung ist zurzeit in erster Linie die Tagesschläfrigkeit der Patienten zu mindern und damit einhergehend die Beeinträchtigungen, wie eine stark verminderte Lebensqualität, Gefährdungen und komorbide Erkrankungen zu umgehen. Dabei ist laut ICSD-3 ein „ungestörter Schlaf“ anzuzielen, welcher per Definition aus unter 15 Apnoe oder Hypopnoen pro Stunde besteht. Die Indikationsstellung ist jedoch bei oligo- oder sogar asymptomatischen Patienten erschwert, wenn die Therapie nicht kurz- oder mittelfristig zu einer Linderung von Beschwerden führt (5). Die am meisten angewendete Therapie für alle Schweregrade der OSA ist die nächtliche Überdruckatmung (19-22). Neben dieser stehen den Patienten zur Behandlung eine Reihe an nicht-Beatmungstherapien zur Verfügung. Aus dem Wissen heraus, dass Übergewicht ein großer Risikofaktor für OSA ist, sind gewichtsreduzierende Maßnahmen, bis hin zur bariatrischen Chirurgie, begleitende Therapiemaßnahmen (23-26). Weiter ist eine Behandlung mit einer Unterkieferprotrusionsschiene (UPS) möglich (6, 27). Auch können bei leicht- bis mittelgradig eingeschränkten Patienten therapeutische Maßnahmen zur Rückenlageverhinderung angebracht sein (28). Chirurgische Verfahren gehören ebenfalls zum Therapiekonzept der OSA. So kann man zwischen resektiven und nichtresektiven Operationsmethoden unterscheiden. Ebenfalls sind gesichtsskelett-verlagernde Maßnahmen (Osteotomien) möglich. Zu den resektiven Verfahren gehört die Uvulopalatopharyngoplastik (UPPP), welche zum Ziel hat, die Obstruktion zu beseitigen bzw. den Luftfluss zu fördern (29). Bei den nicht resektiven Verfahren sind die Radiofrequenzablation (RFTA) und Weichgaumenimplantate zu erwähnen, genauso wie die Stimulation des N. hypoglossus (30-32). Die Indikation für die Einleitung einer Therapie ergibt sich aus der Synopsis von klinischer Anamnese, dem klinisch apparativen Befund, den poly- und/oder auch polysomnographischen Daten, sowie den Begleiterkrankungen des Patienten.

1.2 Ziel der Dissertation

OSA ist eine multifaktoriell bedingte Erkrankung, mit vielfältigen Symptomen und auch diversen komorbiden Erkrankungen. Trotz dessen beruht die Festlegung der Diagnose und auch die Einteilung des Schweregrades auf einem singulären Parameter, dem AHI. Mit dieser Arbeit, sollte an den neuesten, wissenschaftlichen Stand Anschluss genommen werden, dass ein singulärer Parameter zur Beschreibung des Schweregrades einer solch komplexen Erkrankung nicht ausreicht. Dahingehend wurden in einer retroperspektiven Studie, Zusammenhänge zwischen einem möglichen neuen Parameter, der „area under the curve of respiratory arousal“, kurz arousal-AUC und bereits bekannten Parametern, wie dem „hypoxic burden“, AHI und dem „arousal index“ gesucht. Ganz bewusst wurde sich für diese Darstellung ein Verfahren aus dem Bereich des Maschinellen Lernens entschieden, um auch dort an neuste Forschung Anschluss zu nehmen.

Dabei wurde in den polysomnographischen Datensätzen, der von OSA betroffenen Probanden und Probandinnen, eine klinisch bisher nicht beschriebene Auffälligkeit gefunden: Die Mehrheit der Probanden und Probandinnen hatten keinerlei zentralen Apnoen (CAE) im REM-Schlaf. Weiterhin konnte aufgezeigt werden, dass durch die Anpassung der REM-Schlafzeit auf die gesamte Schlafdauer, nur schwer betroffene OSA-Patienten vermehrt CAE im NREM, im Gegensatz zum REM-Schlaf, hatten. Daraus ist eine Folgepublikation entstanden, mit dem Ziel, in einer retroperspektiven, explorativen Studie, diesen neuen Befund zu beschreiben und mögliche, pathophysiologische Erklärungen zu finden.

2 Übersicht über die Publikationen

2.1 A Novel Quantitative Arousal-Associated EEG-Metric to Predict Severity of Respiratory Distress in Obstructive Sleep Apnea Patients

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ORIGINAL RESEARCH
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A Novel Quantitative Arousal-Associated EEG-Metric to Predict Severity of Respiratory Distress in Obstructive Sleep Apnea Patients

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Respiratory arousals (RA) on polysomnography (PSG) are an important predictor of obstructive sleep apnea (OSA) disease severity. Additionally, recent reports suggest that more global indices of desaturation such as the hypoxic burden, namely the area under the curve (AUC) of the oxygen saturation (SaO2) PSG trace may better depict the desaturation burden in OSA. Here we investigated possible associations between a new metric, namely the AUC of the respiratory arousal electroencephalographic (EEG) recording, and already established parameters as the apnea/hypopnea index (AHI), arousal index and hypoxic burden in patients with OSA. In this data-driven study, polysomnographic data from 102 patients with OSAS were assessed (32 female; 70 male; mean value of age: 52 years; mean value of Body-Mass-Index-BMI: 31 kg/m^2). The marked arousals from the pooled EEG signal (C3 and C4) were smoothed and the AUC was estimated. We used a support vector regressor (SVR) analysis to predict AHI, arousal index and hypoxic burden as captured by the PSG. The SVR with the arousal-AUC metric could quite reliably predict the AHI with a high correlation coefficient (0,58 in the training set, 0,65 in the testing set and 0,64 overall), as well as the hypoxic burden (0,62 in the training set, 0,58 in the testing set and 0,59 overall) and the arousal index (0,58 in the training set, 0,67 in the testing set and 0,66 overall). This novel arousal-AUC metric may predict AHI, hypoxic burden and arousal index with a quite high correlation coefficient and therefore could be used as an additional quantitative surrogate marker in the description of obstructive sleep apnea disease severity.

Keywords: sleep apnea, polysomnography, arousal index, area under the curve of arousal, support vector regressor, hypoxic burden, AHI, ODI

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INTRODUCTION

In 2008 it has been stated that 3–7% of adult men and 2–5% of adult women in populations at risk for sleep disordered breathing or cardiovascular diseases have sleep apnea syndrome. There has

The pathogenesis of sleep-disordered breathing is based on central nervous and/or neuromuscular processes that lead to changes in central respiratory regulation and/or upper airway muscle tone during sleep. However, the exact pathogenesis is still the focus of research and not completely understood.

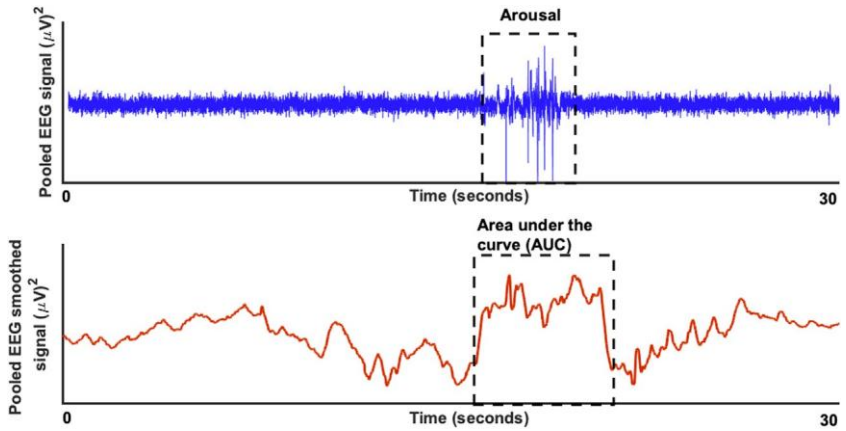

FIGURE 1 | The raw EEG signal (in blue) for a duration of 30 seconds is shown in the top plot with a significant respiratory arousal. In the bottom blot (in red) the smoothed version of the EEG signal is shown to estimate the area under the curve.

been a 14–55% increase in prevalence of obstructive sleep apnea (OSA) over the last 20 years. In particular, patients with cardiovascular disease have been found to have a two- to threefold increased prevalence relative to the normal population (Young et al., 2002; Punjabi, 2008). In a large population-based study ("HypnoLaus study") the prevalence of moderate-to-severe sleep-disordered breathing was even higher, with 23·4% in women and 49·7% in men (Heinzer et al., 2015).

Obstructive sleep apnea is diagnosed using polysomnography (PSG) or home sleep testing (HST). (Markun and Sampat, 2020). In this process, obstructive sleep apnea is diagnosed when the breathing disorder cannot be explained by any other sleep disorder, medical condition, medication, or other substance. In addition, to meet the diagnostic criteria, an apnea-hypopnea index (AHI)

> 15/h (each event lasting ≥10 s) of sleep time or an AHI ≥5/h

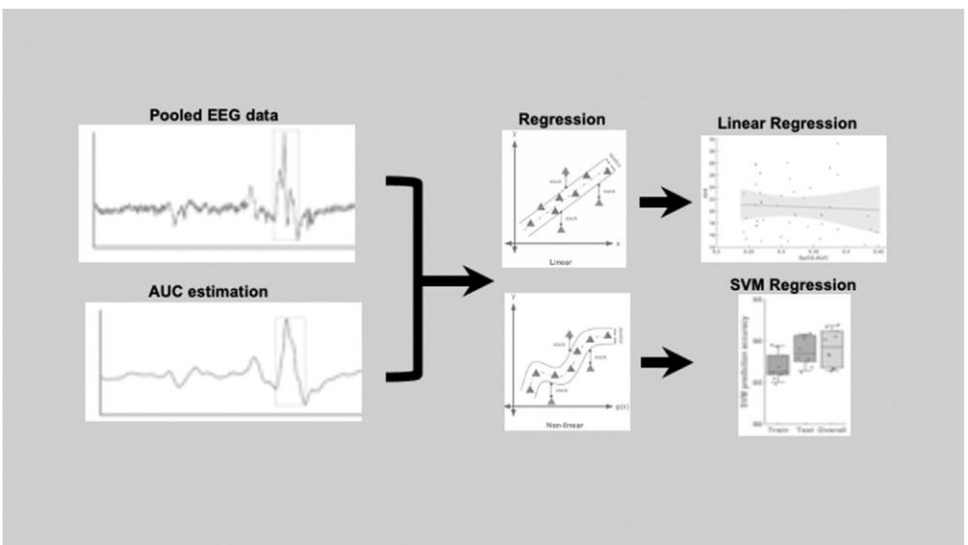

FIGURE 2 | Pipeline figure to show the procedure from the raw EEG data, estimating the area under the curve (AUC) and then followed by the linear as well as the SVM regression.

TABLE 1 | The epidemiological data of the 47 patients with AHI >30/h shows age in years, BMI in kg/m^2, CVRF for the number of cardiovascular risk factors (hypertension, obesity, diabetes mellitus, hyperlipoproteinemia), AHI in number per hour, RDI (Respiratory Disturbance Index) in number per hour, TST (total sleep time) in minutes, ODI (oxygen desaturation index) in number per hour and Arousal Index in number per hour.

	N	Minimum	Maximum	Mean value	Standard deviation
Age (years)	47	28	70	50,17	10,85
BMI (kg/m^2)	47	20,93	46,57	30,99	5,60
CVRF (n)	47	0	3	1,23	0,87
AHI (n/h)	47	14,4	31,3	20,79	4,29
RDI (n/h)	47	15,0	32,7	21,40	4,36
TST (min)	47	202,5	491,0	362,33	54,21
ODI (n/h)	47	1,4	29,8	12,84	7,28
Arousal Index (n/h)	47	4,3	42,5	22,19	7,42

TABLE 2 | The epidemiological data of the 55 patients with AHI between 15 and 30/h shows age in years, BMI in kg/m^2, CVRF for the number of cardiovascular risk factors (hypertension, Obesity, diabetes mellitus, hyperlipoproteinemia), AHI in number per hour, RDI (Respiratory Disturbance Index) in number per hour, TST (total sleep time) in minutes, ODI (oxygen desaturation index) in number per hour and Arousal Index in number per hour.

	N	Minimum	Maximum	Mean value	Standard deviation
Age (years)	55	27	86	52,91	12,94
BMI (kg/m^2)	55	19,57	43,27	31,70	5,12
CVRF (n)	55	0	5	1,77	1,22
AHI (n/h)	55	16,20	130,40	51,07	21,70
RDI (n/h)	55	16,9	130,4	51,89	21,08
TST (min)	55	166,5	458,0	336,86	65,38
ODI (n/h)	55	8,6	97,5	40,44	24,27
Arousal Index (n/h)	55	9,9	93,4	38,19	18,50

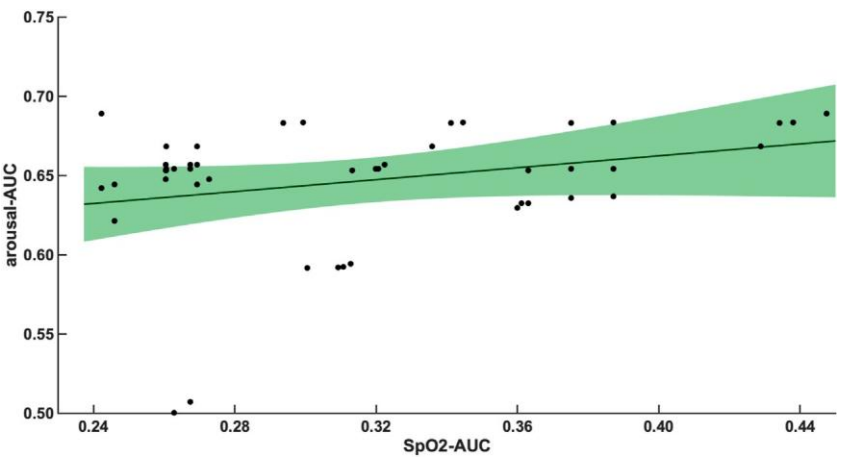

FIGURE 3 | Shows the linear regression results between the arousal-AUC and SpO2-AUC for patients with AHI 15–30/h of TST. The green margins indicate the standard deviation for the correlation and the black dots indicate each subject in this group. r = 0.280/p = 0.056/n = 47.

of sleep time in combination with typical clinical symptoms or relevant comorbidity must be present (Darien, 2014). The evaluation of PSG/HST adheres to the evaluation criteria of the American Association of Sleep Medicine (AASM). The main clinical findings are daytime sleepiness, including involuntary falling asleep, and the AHI, which objectifies the diagnosis and, in conjunction with the clinical symptoms, determines the severity of the disease. An AHI between 15/h and 30/h sleep time classifies OSA as moderate. In the range of an AHI >30/h sleep time, OSA is referred to as severe (Mayer et al., 2016).

However, in recent years, consensus is emerging within the sleep medicine community that the AHI metric may not be sufficient as a singular assessment parameter for classifying the severity of OSA. This metric has many limitations to stand as the sole parameter for defining severity. (Malhotra et al., 2021). Beginning with the fact that there are multiple definitions of hypopnea, the index of apnea and hypopnea provides no

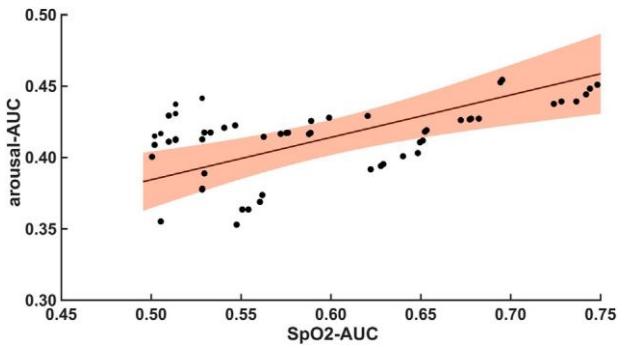

FIGURE 4 | Shows the linear regression results between the arousal-AUC and SpO2-AUC for patients with AHI >30/h of TST. The orange margins indicate the standard deviation for the correlation and the black dots indicate each subject in this group. r = 0.404/p = 0.002/n = 55.

information about the length of each event or the severity of desaturation. Similarly, it is subject to the assumption that apneas and hypopneas should be evaluated equally in their disease- promoting effect (Punjabi, 2016; Randerath et al., 2018). Also, the AHI has a poor correlation with the clinical manifestation of OSA, such as daytime sleepiness, and does not have good predictive power about the risks for cardiovascular disease (CVD) resulting from the condition (Kulkas et al., 2013; Cao et al., 2020).

Therefore, the search for new parameters and novel metrics that provide a more precise prediction of adverse outcomes (cardiovascular, neurocognitive and metabolic, among others) continues. Polysomnography yields a valuable variety of data that should be used to describe the disease. New methods of measurement of respiratory variables and new technologies can better evaluate the different pathophysiological mechanisms underlying OSA (Randerath et al., 2018). One of the new and so far promising parameters in the PSG raw data is the so-called "hypoxic burden" (Cao et al., 2020). Hypoxic burden has been defined as the "total area under the respiratory event-related desaturation curve" (Azarbarzin et al., 2019). Hypoxic burden has been associated with increased CVD mortality in adults aged >40 years in two large cohort studies, namely the Outcomes of Sleep Disorders in Older Men (MrOS) and the Sleep Heart Health Study (SHHS). Higher blood pressure and risk of heart failure in men were also associated with hypoxic burden after eliminating some confounders, such as comorbidities (Azarbarzin et al., 2019; Azarbarzin et al., 2020).

Arousals can be spontaneously, physiologically and an integral part of healthy sleep regulation but also an indication of serious diseases, such as the sleep apnea syndrome we studied (Strollo and Rogers, 1996; Dvir et al., 2018). In 2007, the Arousal Task Force acknowledged in a systematic review that arousal has a major impact on the sleep process. Arousals are scored as an all- or-none event and defined as an abrupt shift of the EEG frequency including alpha, theta and/or frequencies greater than 16 Hz (but not spindles) that lasts at least 3 s, with at least 10 s of stable sleep preceding the change. Patients' subjective and objective excessive daytime sleepiness (EDS), as one of the clinically leading symptoms, correlates positively with EEG arousal count. With increase in EEG arousal number, patients' psychomotor performance also decreases, hormone secretions change, upper respiratory function decreases, sensory arousal threshold increases, and metabolic activity

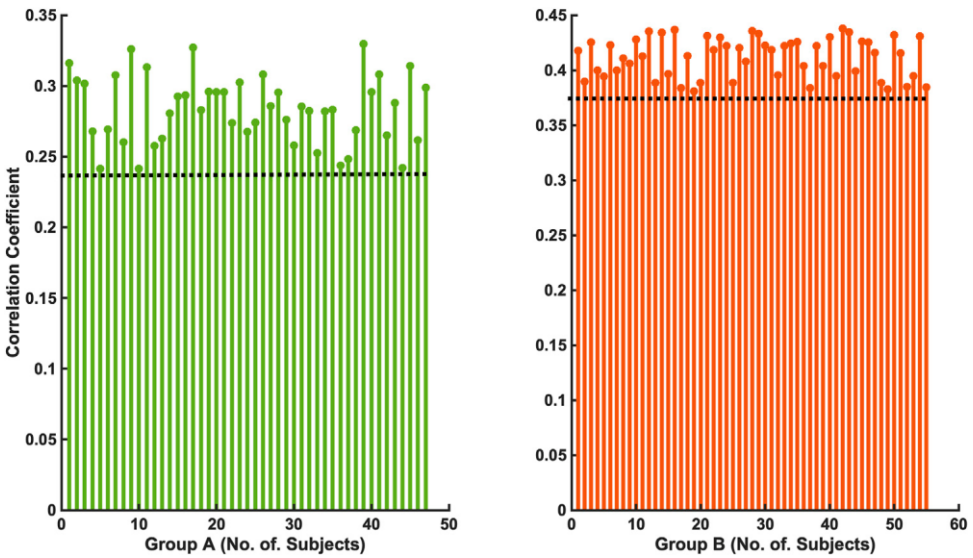

FIGURE 5 | Shows the correlation coefficient between the arousal-AUC and SpO2-AUC for all arousals of every individual of the two separate groups (Group A: AHI 15–30/h of TST; Group B: AHI >30/h of TST).

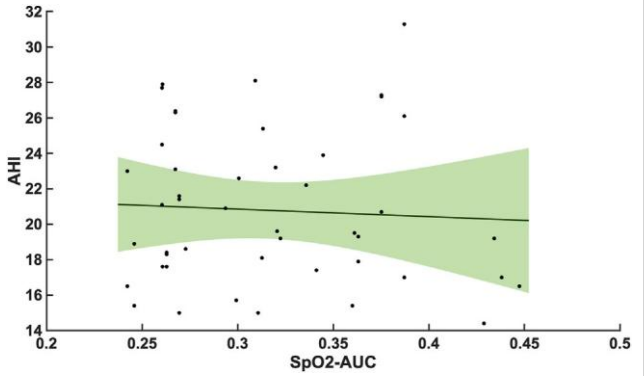

FIGURE 6 | Shows the linear regression results between the AHI and SpO2-AUC for patients with AHI 15–30/h of TST. The green margins indicate the standard deviation for the correlation and the black dots indicate each subject in this group. r = -0,0580/*p* = 0,6987/*n* = 47.

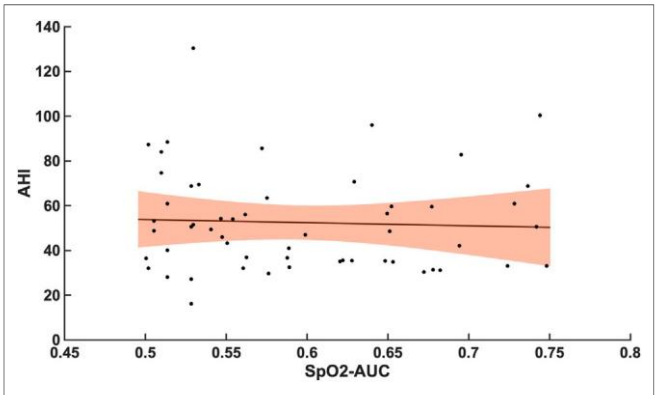

FIGURE 7 | Shows the linear regression results between the AHI and SpO2-AUC for patients with AHI >30/h of TST. The orange margins indicate the standard deviation for the correlation and the black dots indicate each subject in this group. r = -0,0480/*p* = 0.728/*n* = 55.

increases (Bonnet et al., 2007). Chemical factors as blood pressure, CO-2 partial pressure or oxygen saturation are believed to act as stimuli for triggering respiratory arousals (RAs) when reaching a certain threshold value (Younes, 2008). Studies showed that the maximal desaturations of SaO2 during respiratory events with arousals are larger than desaturations in events without arousals (Yan et al., 2016). However, it should be noted that arousal is not only associated with negative effects. The immediate physiological changes associated with arousal are beneficial in rapidly alleviating severe respiratory events and their sequelae (Eckert and Younes, 2014). But among patients the amount of stimuli that lead to an arousal seem to differ, as well as within the same individual for one night (Berry and Gleeson, 1997; Berry et al., 1998; Sforza et al., 1999). Conversely the number of stimuli that lead to an opening of the upper airway differ among individuals; but seem to be fixed regarding any given patient during sleep (Younes et al., 2007; Loewen et al., 2009). Not only the frequency (as depicted by the arousal index), but also the individual intensity of respiratory arousal is quite strong correlated to the OSA severity. Over all there is evidence that the microstructure of respiratory arousals may be patient-specific and that each OSA patient may have a cortical or sub-cortical neural arousal-associated pattern generator, which reacts to an obstructive respiratory event with a stimulus and a specific signature in terms of duration and intensity, like a distinct pattern, in order to ensure ventilation during sleep (Bahr et al., 2021). Overall, it is also not yet fully understood whether it is obstruction per se or the associated hypoxia that leads to arousals.

Overall, however, it can be stated, arousal is an important parameter in understanding the extent to which clinical symptoms are related to respiratory disturbances during sleep and the resulting treatment decisions. The primary aim of our present study was to identify possible associations between the AUC of respiratory arousal as a new metric index and already known parameters such as the hypoxic burden, AHI and arousal index in patients with OSA. Likewise, the arousal-AUC should provide another building block for a better understanding of the origin of arousal. Furthermore, we discuss the results in terms of suggestions for their further clinical use.

MATERIAL AND METHODS

To correlate the area under the curve of the respiratory arousal with the hypoxic burden, AHI and arousal index in OSAS patients, PSG data were used from patients who underwent inpatient polysomnography for the initial diagnosis of obstructive sleep apnea, monitored by sleep medicine qualified personnel. Included in the recording, according to the international AASM standards, were a sleep electroencephalography (EEG), electrooculogram (EOG), electromyography (EMG), electrocardiography (ECG), respiratory flow, snoring, respiratory effort, oxygen saturation, body position, and a video recording during sleep. Nasal airflow was detected by measurement of impact pressure through a nasal sensor that determined pressure fluctuations of the breathed air stream. Thoracic and abdominal excursions, oxyhemoglobin saturation (pulse oximeter) and body position were simultaneously recorded. Snoring was recorded with a pre-laryngeally fixed microphone. The sampling frequency of the EEG data was 200 Hz. The data was high pass filtered at 0.1 Hz and was not resampled before the analyses. The two central channels (C3 and C4) were used for the analysis with the knowledge that many sleep laboratories around the world still use the Rechtschaffen & Kales EEG recordings (Kales and Rechtschaffen, 1968). The polysomnographic recordings were performed using the Alice-LE-Diagnostic Sleep System (Philips Healthcare/Respironics, Best, Netherlands as supplied by Loewenstein Medical, Bad Ems, Germany). In all patients, two PSG were performed on two consecutive days, and only the second night was used for the analysis of the data in each case to minimize any potential first-night effect on sleep efficiency and potentially minimize the possibility of missing a severe OSAS in the diagnosis (Gouveris et al., 2010). In the morning following each sleep study night, sleep stages and sleep-related respiratory events were manually scored according to the American Academy of Sleep

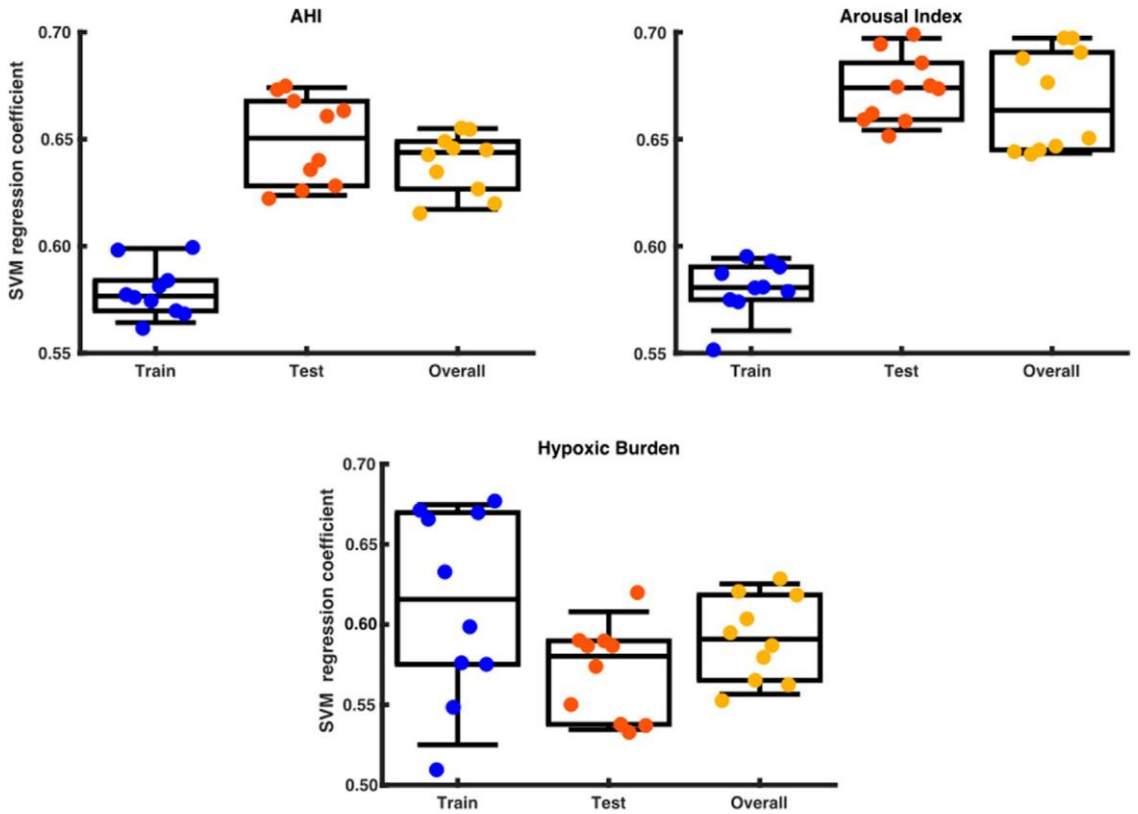

FIGURE 8 | Box plot with the distribution of a data set. The x axis shows the division into training set, test set and overall testing. The y-axis shows the SVM correlation coefficient.

Medicine (AASM)-2012 guidelines (Berry et al., 2012). This was performed visually by sleep medicine board-certified specialists. Nasal airflow amplitude reduction greater than 90%, lasting for at least 10 s, was defined as apnea. Hypopnea was defined as an airflow reduction between 50 and 90% with an associated 3% reduction of the blood oxygen saturation (SpO2). Apnea events were further classified into obstructive, central, or mixed based on simultaneous evaluation of nasal airflow and thoracic and abdominal excursion. Physiological EEG arousals (e.g., the one associated with changes in sleep stage) and motor-related arousals were excluded in this study.

Each patient also underwent a clinical examination prior to polysomnography, which adhered to the criteria of the DGSM (German Society for Sleep Research and sleep medicine) S3 guideline 2017 which is based on the guidelines of the AASM Manual for the scoring of sleep and associated events (Berry et al., 2012; Mayer et al., 2016).

Criteria for data inclusion and analysis, were a first diagnosis of OSAS with an AHI ≥15/h. Exclusion criteria were age <18 years, active malignant tumors (end of last therapy <5 years), COPD (Gold 2–4), Raynaud's syndrome (due to problems with oxygen saturation measurement), congestive heart failure (NYHA III or IV), severe psychiatric illness, severe insomnia or pre-existing therapy for a known OSAS. Approval for the study was provided by the local Institutional Review Board (Nr. 2018–13942). The research findings presented in this manuscript are based on research and clinical practices that conform to the principles of the Helsinki Declaration.

Figure 1 shows an example of a pooled EEG trace in the top plot and the smoothed curve below from which the area under the curve was estimated. The pooling was done to increase the signal-to-noise ratio for the further analyses of area under the curve (AUC). In this study, the technique used was pooling together signals from multiple EEG channels (C3 and C4) weighted by their respective signal-to- noise (SNR) relative to the overall SNR of both the channels. The SNR was estimated in the raw signal, by taking "signal" component as the mean ±2 standard deviation and the "noise" component as the mean ±0,5 standard deviation. The values to indicate the SNR's for each channel separately were: C3 (24,42 ± 4,84)dB, C4 (22,39 ± 5,51)dB and for the pooled signal SNR (31,23 ± 3,15)dB. The EEG signal was then smoothed based on the 200-time points average (sampling frequency of 200 Hz) equivalent to one second epochs. After the smoothing the area under the curve was determined based on the starting and end point was manually marked for each arousal. The slope was estimated from the starting point to the neighboring peak and followed by estimation of the AUC as illustrated in the schematic Figure 1. Here, we performed both a linear regression as well as a support vector regressor (SVR) analysis, representing a machine learning-based multiple regression method that could associate the observed and trained values and present the correlation coefficient as

a prediction (Drucker et al., 1996). Figure 2 shows the procedure from the raw EEG data, estimating the area under the curve (AUC) and then followed by the linear as well as the SVM regression. To create a better comparison, we not only created a correlation between arousal-AUC and SpO2-AUC, but also between AHI and SpO2-AUC.

In this study, a data-driven regression model was implemented without explicitly stating a functional form indicating a nonparametric technique. In short, the algorithm looks for an optimally separating threshold between the two data sets by maximizing the margin between classes' closest points. The points lying on the boundaries are called support vectors, and the middle of the margin is the optimal separating threshold. In most cases the linear separator is not ideal; therefore, a projection into a higher- dimensional space is performed where the data points effectively become linearly interrelated. Here, we have used the RBF kernel for this projection due to its good performance as discussed in Cortes and Vapnik (1995) and based on previous application of support vector machines in earlier studies (Cortes and Vapnik, 1995; Muthuraman et al., 2016; Michels et al., 2017; Michels et al., 2021). Then used the grid search (min = 1; max = 10) to find the few optimal input regularization parameters, namely C (Type of classification algorithm), which is the capacity constant. The parameter C should be carefully chosen because the larger the C, the more the error is penalized (i.e., leads to over-fitting) so we tested values in the range of 1–1,000 and choose a gamma of 0.25 for the RBF kernel function (which represents the data for the cross validation). The selection was checked by 10-fold cross-validation by taking 75% of the data set for training and 10% for testing. A soft-margin classifier of the calculated independent variables was used for every parameter and spurious correlations (correlations which could be due to artifacts) were weighted by a penalty constant P. To optimize correlation coefficient, this was calculated for every regressor. To demonstrate that no over-fitting is attested in our data for the SVM regression algorithm, we performed cross validation. The results from the SVM were reported here with 10-fold cross validation.

RESULTS

For prediction using support vector regressor analysis, PSG data from a total of 102 patients were included. Within these 102 patients, there were 47 patients with moderate severity (AHI between 15 and 30/h of total sleep time). Of these, 27 patients were male and 20 patients were female. The remaining 55 patients were severely affected with an AHI
>30/h of total sleep time. Among these, 43 were male and 12 were female patients. Table 1 and Table 2 show further epidemiological data for the above patients separated by the two groups (Table 1 for the group with AHI >30/h and Table 2 for the group with AHI between 15 and 30/h).

The 47 patients with moderate severity of AHI between 15 and 30/h of total sleep time, showed a weak and non-significant correlation between the arousal-AUC of EEG C3/C4 pooled trace and SpO2-AUC of PSG (r = 0.280; p = 0.056), which is shown in Figure 3. In contrast, the remaining 55 severely affected patients, with an AHI >30/h of total sleep time, showed a significant correlation in linear regression of the arousal-AUC of EEG C3/C4 pooled trace and SpO2-AUC of PSG (r = 0.404; p = 0.002), shown in Figure 4. Figure 5 shows the correlation coefficient between the arousal-AUC and SpO2-AUC for all arousals of every individual of the two separate groups.

Compared with the correlation between arousal-AUC and SpO2-AUC, the correlation between AHI and SpO2-AUC offered no to little linear correlation for both groups and did so without significance (group A [r = -0,0580; p = 0,6987] and group B [r = -0,0480; p = 0.728]). Figure 6 and Figure 7 show the linear regression results between the AHI and SpO2- AUC for both groups.

By using a support vector regressor (SVR) analysis with the arousal-AUC metric we could predict the AHI with an correlation coefficient of 0,58 in the training set, 0,65 in the testing set and 0,64 overall. The hypoxic burden showed a correlation coefficient of 0,62 in the training set, 0,58 in the testing set and 0,59 overall. The arousal index had a correlation coefficient to the arousal-AUC metric of 0,58 in the training set, 0,67 in the testing set and 0,66 overall. Figure 8 shows a box plot with the distribution of a data set.

DISCUSSION

Our results show that using an SVR with the arousal-AUC metric results in very high predictive power for the AHI, hypoxic burden, and arousal index and therefore could be used as an additional quantitative surrogate marker in the description of obstructive sleep apnea respiratory disease severity.

A significant correlation between the arousal-AUC and SpO2- AUC was found in patients with AHI >30/h than in patients with AHI between 15/h and 30/h. Therefore, especially in OSAS patients with severe respiratory distress, a novel positive correlation between the hypoxic burden, as represented by the SpO2-AUC-metric, and the severity of arousal (as represented by the arousal-AUC) was found (Figures 3, 4). In comparison, we were able to show with the data that the AHI to SpO2-AUC offered no significant correlation. This again underlines, as described in the introduction, that the AHI as a singular parameter is not suitable for the description of obstructive sleep apnea and is inferior to new parameters, which could be used complementarily. To further understand the origin of arousal, this correlation can serve as another building block to show that there is a close relationship between hypoxia and arousal. However, it cannot be used to conclude a causal relationship.

Given that hypoxic events usually temporally precede respiratory arousals in OSAS patients, it may well be argued that the greater the hypoxic burden, the greater becomes the central nervous system (CNS) drive trying to compensate the hypoxic burden by means of an arousal. To our knowledge, there are no previous reports on such a correlation. There is a much lesser degree of this precise correlation in OSAS patients with moderate (AHI = 15–30/h) respiratory distress. This suggests that, in OSAS patients with moderate respiratory disease severity the degree and/or the temporal extent of oxygen desaturations may exert a much less significant stimulatory influence on the

CNS arousal-generating drive than in patients with severe OSAS. As a result, either different pathophysiologic mechanisms or dose-effect responses regarding regulation of arousal features by hypoxia in OSAS may exist in patients with different degrees of respiratory OSAS severity.

Younes et al. showed that the average arousal intensity is not related to the magnitude of the preceding respiratory stimuli but was positively associated with arousal duration, time to arousal, rate of change in epiglottic pressure, and negatively with body mass index ($R2 > 0.10$, $p \leq 0.006$). The authors concluded that the average arousal intensity is independent of the preceding respiratory stimulus. (Younes, 2004). The same could be observed in other studies (Amatoury et al., 2016). It is also noted that respiratory-induced cortical arousals occur during inspiration as well as expiration but differ in the increase of the tensor palatini muscle activity and minute ventilation (Amatoury et al., 2018). With the knowledge from recent studies that arousal has a strong correlation with sympathetic hyperactivity in OSA patients and thus a possible component in pathophysiological cause, it can be assumed that also here, similar to the AHI, not only the total number of events, but the microstructure of the event plays a significant role in the disease process (Kim et al., 2019; Ferreira et al., 2020). Given the good correlation coefficient between AUC-arousal and the AHI, hypoxic burden, and the arousal index, it may be assumed that AUC-arousal is related to the severity of OSA. These facts support the hypothesis that not only the intensity alone or duration alone of an arousal, but the whole microstructure is relevant to understand the possible arousal "burden".

One strength of the study is that we used a pooled C3- and C4- EEG signal for the analysis of the data, which resulted in optimal use of the available information provided by any one of the two brain hemispheres (Prucnal and Polak, 2019). The data originated from a rather large group of 102 patients. A very homogeneous distribution of the measured values in terms of AHI, age, and BMI resulted. A weakness of this study is that no mildly affected patients with an AHI <15/h were studied; nonetheless, we have made the conscious decision not to study such a group of patients from the very beginning because we knew from previous research and our own experience that such patients have much less frequent arousals, making statistical analysis of arousals in such a mild OSA patient subgroup quite difficult or impossible. Additionally, a larger patient population would of course further enhance the correlation coefficient, as well as the results of the SVM.

Support vector machine algorithms have been increasingly applied in medical data during the past few years since they can provide systematized architecture for analyzing and extracting important information from complex data (Divya and Sonali, 2013; Huang et al., 2020). For this reason, a support vector regressor analysis was deliberately chosen in this study, on the one hand with the intention of making the best possible prediction, and on the other hand to demonstrate the possibilities provided by machine learning methods. In the future, this could also improve and simplify the previous, visually manual analysis of polysomnography.

A larger cohort would be needed to improve the power of the study. Future studies should further dissect the microstructure of arousal and compare it with symptomatic components of OSA. Given the myriad of OSA-associated conditions across multiple biological systems, one might expect the optimal metric of OSA severity to differ depending on the outcome of interest (Malhotra et al., 2021).

CONCLUSION

Given that traditional metrics, such as the AHI or oxygen desaturation index (ODI), increasingly appear to be insufficient to capture the complexity of the OSAS disorder in many patients, the arousal-AUC metric may provide a novel additional strong correlate for the hypoxic burden that should be validated in further studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Medical Ethics Committee of the Rhineland- Palatinate State (2018-13942). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MM provided data extraction, analysis, designed the figures and revised the manuscript. DH and KN helped in data analysis. GH is responsible for study conception and design, helped in preparing the introduction and the discussion and revised the manuscript. M-ES collected the data, performed data analysis, created the tables, wrote, and revised the manuscript. BK, HT, and KL reviewed and revised the manuscript. All authors approved the submitted version of the manuscript and take full responsibility for it. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

2.2 Central Apneic Event Prevalence in REM and NREM Sleep in OSA Patients: A Retrospective, Exploratory Study

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Central Apneic Event Prevalence in REM and NREM Sleep in OSA Patients: A Retrospective, Exploratory Study

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Simple Summary: Obstructive sleep apnea is the most common breathing-related sleep disorder. In addition to the quantitatively dominant obstructive apneas, patients may also be affected by central apneas. This study investigates the frequency of occurrence of central apneas in REM and NREM sleep in patients suffering from OSA of varying severity. When adjusted for the respective REM and NREM sleep duration, a significantly increased frequency of CAEs in NREM was found only in severely affected OSA patients.

Abstract: Patients with sleep-disordered breathing show a combination of different respiratory events (central, obstructive, mixed), with one type being predominant. We observed a reduced prevalence of central apneic events (CAEs) during REM sleep compared to NREM sleep in patients with predominant obstructive sleep apnea (OSA). The aim of this retrospective, exploratory study was to describe this finding and to suggest pathophysiological explanations. The polysomnography (PSG) data of 141 OSA patients were assessed for the prevalence of CAEs during REM and NREM sleep. On the basis of the apnea–hypopnea index (AHI), patients were divided into three OSA severity groups (mild: AHI < 15/h; moderate: AHI = 15–30/h; severe: AHI > 30/h). We compared the frequency of CAEs adjusted for the relative length of REM and NREM sleep time, and a significantly increased frequency of CAEs in NREM was found only in severely affected OSA patients. Given that the emergence of CAEs is strongly associated with the chemosensitivity of the brainstem nuclei regulating breathing mechanics in humans, a sleep-stage-dependent chemosensitivity is proposed. REM-sleep- associated neuronal circuits in humans may act protectively against the emergence of CAEs, possibly by reducing chemosensitivity. On the contrary, a significant increase in the chemosensitivity of the brainstem nuclei during NREM sleep is suggested.

Keywords: central sleep apnea; sleep stages; polysomnography; chemosensitivity; obstructive sleep apnea; REM sleep

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1. Introduction

Obstructive sleep apnea (OSA) is a common disorder in the general population. It may be present both in patients without other pre-existing conditions as well as in patients with comorbidities, e.g., heart failure. OSA is associated with increased cardiovascular risk [1,2] The disease itself has a strong negative effect on the health, alertness, and productivity of patients [3]. In a large population-based study ("HypnoLaus study") in central Europe, the prevalence of moderate-to-severe sleep-disordered breathing in the adult general popu- lation was quite high, being 23.4% in women and 49.7% in men [4]. The severity of the disease is associated with a variety of individual risk factors, such as age, body mass index

(BMI), smoking, and alcohol consumption [5]. Obstructive sleep apnea is diagnosed in the clinical routine using polysomnography (PSG) or home sleep testing (HST). In this process, obstructive sleep apnea is diagnosed when the breathing disorder cannot be explained by any other sleep disorder, medical condition, medication, or other substance. In addition, an apnea–hypopnea index (AHI) ≥ 15/h (each event ≥ 10 s) sleep time or an AHI ≥ 5/h sleep time in combination with typical clinical symptoms or relevant comorbidity must be present [6]. The pathogenesis of OSA is based on complex central nervous and/or neu- romuscular processes that lead to changes in central respiratory regulation and/or upper airway muscle tone during sleep [7–9]. In this context, it is known that the severity of OSA between sleep stages, within an individual, can vary considerably [10,11]. Some studies have tried to elucidate the mechanisms underlying the dependence of OSA severity on sleep stages. The focus has been on the main pathophysiological mechanisms of the disease. These include upper airway collapsibility, muscle responsiveness, arousal threshold, and ventilatory control stability (loop gain) [7,8]. Loop gain is defined as the corrective respi- ratory response divided by the magnitude of the respiratory disturbance that produced the correction. A large respiratory response to a small perturbation corresponds to a high loop gain and significantly represents unstable respiratory control. One pathophysiological trigger of a high loop gain is excessive chemosensitivity to CO_2 above and below the level of eupnea [12]. However, the data available to date are very limited in terms of allowing any firm conclusions to be drawn [13–17]. It has been shown that the severity of SDB, in terms of increased AHI, increases in sleep stage N1/N2 compared to N3 (slow wave sleep) [18]. A total of 55% of OSA patients have a prominent increase in the obstructive apneic events (OAEs) during NREM sleep stages compared to REM. However, also, a greater AHI in REM compared to NREM can be a part of the clinical spectrum of OSA, which is called REM-related OSA [19,20]. In mild-to-moderate OSA, there is a wide heterogeneity in the patterns of disease, and thus OSA has been categorized into discrete disease phenotypes such as supine-predominant OSA, REM-predominant OSA, NREM-predominant OSA, or intermittent OSA [21].

In patients with central sleep apnea (a sleep disorder with high loop gain), the breath- ing disorder often becomes evident in NREM sleep [22]. Similar to our observations in the present study, it has been previously suggested that central apneas may be completely absent in REM sleep [23]. Central sleep apnea is described as a break in airflow during sleep, without associated respiratory effort. Often central sleep apnea occurs as a cyclic alternation of periods of hyperventilation, with periods of apnea, known as Cheyne–Stokes breathing. A further criterion for the diagnosis of central apneic events (CAEs) is a duration of 10 s or more on polysomnography. In clinical practice, patients show not only features of one breathing disorder, but a mixture of obstructive sleep apnea and central apneas. The proportion of the two features may change during the night. For this reason, one often speaks of an overlap of obstructive sleep apnea with central sleep apnea [22]. In our exploratory observation, we found a relatively large cohort of patients who had predominant OSA and showed a complete absence of CAEs in the REM sleep phase. Additionally, when adjusted for the respective REM sleep duration, an increased number of CAEs in NREM was found only in the group of patients severely affected by OSA. The aim of the study was to describe and compare the phenomenon of the frequency of central apneic events occurring in patients suffering from OSA in different degrees of severity in REM and NREM sleep, taking into account the duration of the sleep phases.

2. Materials and Methods

In this exploratory study, we used a sample size of 141 patients who underwent inpatient polysomnography for the initial diagnosis of obstructive sleep apnea. Included in the recording, according to current AASM (American Academy of Sleep Medicine, Inc., Darien, IL, USA) standards, were a sleep electroencephalography (EEG), electrooculogram (EOG), electromyography (EMG), electrocardiography (ECG), respiratory flow, snoring, respiratory effort (measured by respiratory impedance plethysmography, by using thoracic

and abdominal belts), oxygen saturation, body position, and a video recording during sleep. Nasal airflow was detected by measurement of impact pressure through a nasal sensor that determined pressure fluctuations of the breathed air stream. Thoracic and abdominal excursions, oxyhemoglobin saturation (pulse oxymeter), and body position were simultaneously recorded. Snoring was recorded with a pre-laryngeally fixed microphone. The sampling frequency of the EEG data was 200 Hz. The data were high pass filtered at 0.1 Hz and were not resampled before the analyses. The polysomnographic recordings were performed using the Alice-LE-Diagnostic Sleep System (Philips Healthcare/Respironics, Best, the Netherlands).

All patients had presented to our outpatient department in the Sleep Medicine Cen- ter of a tertiary University Medical Center with complaints of snoring and or breathing cessation during sleep reported by their partner or peers. Additionally, all patients had previously undergone an ambulatory HSAT (home sleep apnea testing) by a primary physi- cian that showed an AHI > 5/h. As a consequence, each patient's PSG was recorded over two nights to circumvent the first night effect and only the data from the second night were used for further analysis [24]. The PSG data were evaluated and visually scored by sleep- medicine-board-certified specialists according to current AASM guidelines [13]. Nasal airflow amplitude reduction greater than 90%, lasting for at least 10 s, was defined as apnea. Hypopnea was defined as an airflow reduction between 50 and 90% with an associated 3% reduction of the blood oxygen saturation (SpO2). Apnea events were further classified into obstructive, central, or mixed on the basis of simultaneous evaluation of nasal airflow and thoracic and abdominal excursion. Physiological EEG arousals (e.g., the one associated with changes in sleep stage) and motor-related arousals were excluded in this study. Each patient underwent a clinical examination prior to polysomnography in accordance with the criteria of the AASM. The clinical examination was performed by trained (specialist) physicians who were not identical to the experts who selected the patient data for the study. To determine the degree of excessive daytime sleepiness, the Epworth Sleepiness Scale (ESS), a self-completion test, was used [25]. Inclusion and exclusion criteria were carefully considered for the patient. Inclusion criterion for data and analysis selection was the diagnosis of OSA. Exclusion criteria were age < 18 years, active malignant tumors (end of definitive oncologic therapy > 5 years), chronic obstructive pulmonary disease (COPD, Gold stages 2–4), Raynaud's syndrome (due to problems with oxygen saturation measure- ment), primary CSA, pulmonary hypertension, Arnold–Chiari malformation, sedating medication, severe psychiatric illness, severe insomnia requiring treatment, congestive heart failure (NYHA III or IV), or pre-existing therapy for OSA (e.g., surgery or positive airway pressure therapy), as well as an AHI < 5/h. PSG data from 141 patients suffering from OSA were retrospectively analyzed for the occurrence of central apneas during both REM and NREM sleep. The 141 patients were divided into three groups on the basis of the severity of OSA: mildly affected (AHI 5/h to < 15/h), moderately affected (AHI 15/h to <30/h), severely affected (AHI > 30/h). The collection of data and their analysis are compatible with the principles of the Declaration of Helsinki and approved by the local Institutional Review Board (no. 2018-13942).

As expected, NREM sleep time was much longer than REM sleep time in all subjects. As a result, in the relatively shorter REM sleep duration, even fewer of the already rare central apnea events could be observed. In order to avoid distortions of the data and to evaluate the data conservatively rather than inflating them, we calculated the apnea events in relation to the respective REM sleep duration of each individual. For our calculations, we related the number of central apneic events of each patient to the individual duration of the REM phase (i.e., not to the average in the group) and thus considered each patient individually. Important in this context is that we compared the number of central apneic events (CAEs) as absolute events only within one group of patients, i.e., we compared the number of CAES only within the group of mildly (or moderately or severely) affected patients between REM and NREM sleep. Thereby, we always considered the total sleep time in REM and NREM. Since the proportions of REM and NREM in TST are known to

be very different and thus counting only the CAEs in the respective sleep phases does not lead to comparable results, we normalized the duration of NREM and REM to look at sleep times of equal duration (with respect to REM duration). That means we calculated how many CAEs would have occurred in one (calculated) NREM duration if it corresponded to the REM duration. If this normalization is not performed, a comparison of absolute events is difficult because the share of the NREM phase in the total sleep time is significantly larger than the share of the REM phase in the total sleep time. Therefore, the total REM duration of the patient was taken into account, and the number of CAEs in a normalized NREM duration was calculated according to the following equation:

$$(Number\ of\ CAEs\ in\ REM)_{norm} = \frac{Number\ of\ CAEs\ in\ NREM}{Duration\ NREM\ [h]} \times Duration\ REM\ [h] \quad (1)$$

The normalized (time adjusted) events of CAEs in NREM and REM nested in the three main groups were compared using Wilcoxon's rank sign test. We used a global Kruskal–Wallis test to analyze the overall difference between groups. A significant global test with a p-value < 0.05 was followed by a post hoc analysis using the Wilcoxon test comparing the adjusted frequency of NREM and REM events within the three OSA severity groups. Post hoc p-values were corrected for multiple comparisons using the Bonferroni correction. We considered a Bonferroni–Holm-corrected p-value of 0.05 to be significant. For the comparison of the parametric data (Shapiro–Wilk test) that showed equal variance (Bartlett's test for homogeneity) across groups (Table 1) between the three groups, we used ANOVA (analysis of variance) for global testing and Tukey's HSD test for post hoc comparison (Table 1), while non-parametric data were analyzed using Wilcoxon's signed rank sum test followed by post hoc testing by Wilcoxon's test of the mildly affected group against the other two groups (Table 2).

Table 1. The epidemiological data of the 141 patients divided in the severity groups (mild, moderate, and severe) showing the variables age in years, BMI in kg/m^2, ESS (Epworth Sleepiness Scale) on a scale from 0 to 24, TST (total sleep time) in minutes, TST in REM as a percentage, the proportion of sleep time in supine position of TST as a percentage, and the sleep efficiency as a percentage. The CVRF value stands for the number of cardiovascular risk factors. These were counted according to the patient's health history (e.g., hypertension, obesity, hyperlipoproteinemia, diabetes mellitus). If the patient has two risk factors, the CVRF value is equal to 2. Besides the grouping, the number of patients, the mean value, the standard deviation, and the upper/lower 95% confidence interval are shown. To test for significance, the analysis of variance (ANOVA) was used together with the Tukey HSD test. We compared the moderately and severely affected groups against the mildly affected group. n.s.: not significant.

Variable	Severity Group	Number	Mean Value	Standard Deviation	95% Confidence Interval Lower Limit	95% Confidence Interval Upper Limit	Global Testing (ANOVA)	Post Hoc (All Pairs Tukey) against "Mild"
Age (years)	mild	40	46.25	14.58	41.57	50.92	n.s.	
	moderate	47	50.54	11.25	47.25	53.86	n.s.	
	severe	55	52.75	13.04	49.22	56.26	n.s.	
BMI (kg/m^2)	mild	36	26.54	4.69	24.96	28.15	<0.0001	
	moderate	47	30.99	5.60	29.35	32.62	<0.0001	0.0005
	severe	55	31.69	5.11	30.32	33.09	<0.0001	<0.0001
ESS	mild	14	9.13	4.35	6.62	11.64	n.s.	
	moderate	45	9.8	4.76	8.37	11.22	n.s.	
	severe	54	10.15	5.17	8.72	11.55	n.s.	
CVRF (count)	mild	40	0.93	0.93	0.61	1.23	0.0005	
	moderate	47	1.22	0.87	0.97	1.49	0.0005	0.0274
	severe	53	1.76	1.22	1.44	2.11	0.0005	0.0004
TST (min)	mild	40	362.09	55.54	344.31	379.84	0.0483	
	moderate	47	362.33	54.21	346.39	378.25	0.0483	n.s.
	severe	55	336.84	65.37	319.18	354.52	0.0483	n.s.
REM in TST (%)	mild	40	15.32	5.77	13.46	17.15	0.001	
	moderate	47	13.36	6.17	11.53	15.16	0.001	n.s.
	severe	55	10.62	6.11	8.97	12.27	0.001	0.0008

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Table 1. *Cont.*

Variable	Severity Group	Number	Mean Value	Standard Deviation	95% Confidence Interval Lower Limit	95% Confidence Interval Upper Limit	Global Testing (ANOVA)	Post Hoc (All Pairs Tukey) against "Mild"
Supine Pos. in TST (%)	mild	40	32.35	25.44	24.19	40.49	0.0213	
	moderate	47	46.47	27.48	38.39	54.55	0.0213	n.s.
	severe	55	47.56	30.32	39.36	55.74	0.0213	0.0273
Sleep efficiency (%)	mild	40	77.38	11.62	73.68	81.11	0.003	
	moderate	47	85.76	8.57	83.24	88.28	0.003	
	severe	55	81.52	12.77	78.08	84.97	0.003	0.0002

Table 2. The epidemiological data of the 141 patients divided in the severity groups (mild, moderate, and severe) showing the variables AHI in number per hour, Respiratory Disturbance Index (RDI) in number per hour, duration of SpO2 < 90% as a percentage of TST, mean SpO2 in NREM as a percentage, and mean SpO2 in REM as a percentage. Besides the grouping, the median with 25/75 percentile is shown. To test for significance, the Wilcoxon rank-sum test as well as the post hoc Wilcoxon test was used. We compared the moderately and severely affected groups against the mildly affected group.

Variable	Severity Group	Median	25th Percentile	75th Percentile	Global Testing Wilcoxon Rank Sum	Post hoc Wilcoxon against "Mild"
AHI (n/h)	mild	6.2	4.1	10.7	0.0001	
	moderate	19.5	17.6	23.9	0.0001	0.0001
	severe	48.6	34.9	60.9	0.0001	0.0001
RDI (n/h)	mild	7.5	4.5	11.5	0.0001	
	moderate	20.8	17.6	24.4	0.0001	0.0001
	severe	48.6	36.1	60.9	0.0001	0.0001
Duration < 90% SpO2 (%)	mild	0.08	0.00	0.74	0.0001	
	moderate	0.78	0.15	2.44	0.0001	0.0004
	severe	3.74	0.74	13.08	0.0001	0.0001
Mean SpO2 in % NREM (%)	mild	95	94	96	0.0001	
	moderate	94	93	95	0.0001	0.0043
	severe	93	92	94	0.0001	0.0001
Mean SpO2 in % NREM (%)	mild	95	93	96	0.0001	
	moderate	94	93	96	0.0001	0.0010
	severe	93	91	95	0.0001	0.0001

3. Results

Patients in the three severity groups were proven to have similar epidemiological data on average (Tables 1 and 2). We compared the groups against each other, and it was noticeable that the comparison of age, in contrast to BMI, was shown to be non-significant (Table 1). This observation is not consistent with the prevailing hypothesis that OSA is an age-dependent disease [26–29]. However, we considered a comparatively small number of cases, which is not suitable to test this hypothesis. In addition, on the basis of the data of the medical records, it turned out that there were no patients with diagnosed heart failure of any degree in any of the three subgroups of our cohort.

The mild severity group included 40 patients, of whom 35% were female. Of the 47 patients suffering from moderate OSA, 42.6% were female, and of the 54 patients with severe OSA, 22.2% were female. On the basis of a thorough analysis of the raw data, it turned out that the vast majority of the patients (73.8% of the total 141 patients) had no CAEs during REM sleep at all. In addition, this phenomenon has been observed in each one of the three groups separately: 67.5% of patients with mild OSA showed no CAEs at all in REM sleep, whereas this phenomenon was more prevalent in moderately (80.9%) and severely affected (74.1%) OSA patients. Of note, the proportional duration of the REM sleep phase in relation to the total sleep time (TST) varied significantly among patients and ranged between 2.2% and 24.9% (mean value = 12.9 ± 6.3%) of TST.

When taking into account this aspect for the data analysis, i.e., if the absolute number of CAEs is related to the duration of the REM phase, then the frequency (number of events divided by time) of CAEs in the REM phase did not differ significantly between the three patient severity groups (mildly, moderately and severely affected) (Figure 1). However, when adjusted for the (individual) duration of the REM sleep phase within the same patient

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group, the frequency of CAEs in the NREM phase was significantly increased compared to the frequency of CAEs in the REM phase in the group of severely affected patients (p = 0.0006). The latter finding was not evident either in the moderately (p = 0.1111) or in the mildly (p = 0.1158) affected group (Table 3).

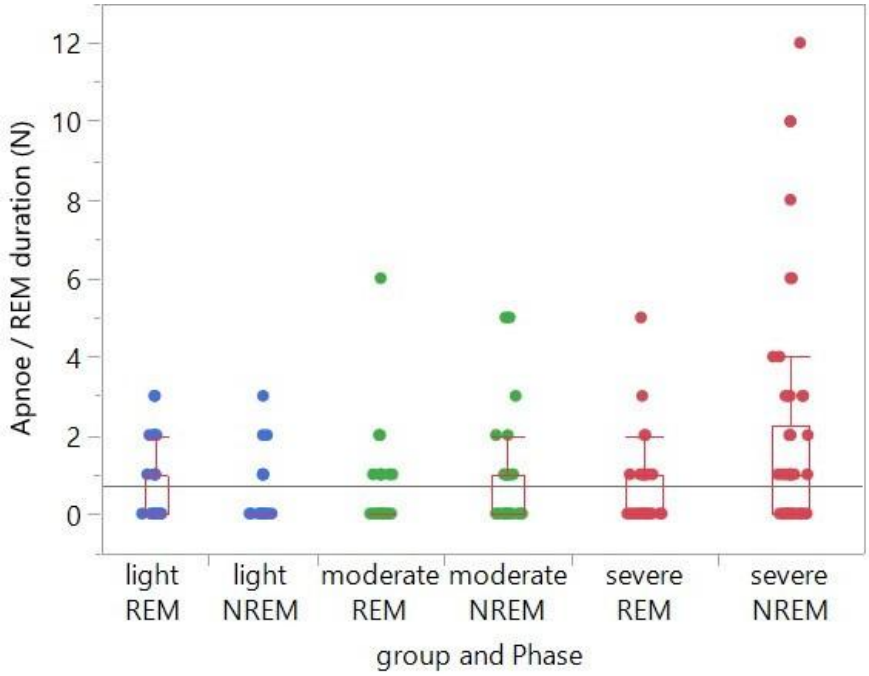

Figure 1. Single factorial analysis of the number of central apneic events (CAEs) in relation to the respective REM sleep duration by group (severity of OSA: mild, moderate, severe) and sleep phase (REM, NREM). In the group of severely affected OSA patients, the frequency of CAEs was significantly increased in the NREM phase when compared to the one in the REM phase, when adjusted for the duration of the REM phase. This was not the case in the group of moderately and mildly affected OSA patients. The symbols overlap in many cases, and most data points were at the value 0. Unfortunately, it is difficult to present this clearly without distorting the intended message of the plot. Due to the overlay, not all data points are clearly visible.

Table 3. Single factorial analysis of the number of central apneic events (CAEs) in relation to the respective REM sleep duration by group (severity of OSA: mild, moderate, severe) and sleep phase (REM, NREM).

Category 1	Category 2	Mean Score Difference	Standard Error Difference	Z-Score	p-Value
Severe NREM	Severe REM	18.1418	5.306820	3.41978	0.0006
Moderate NREM	Moderate REM	6.9362	4.353624	1.59320	0.1111
Mild NREM	Mild REM	−6.2000	3.942024	−1.57280	0.1158

In the performed correlation analyses, we were unable to find any correlation of this phenomenon (an increased number of CAEs in NREM sleep in patients with severe OSA) with other parameters (age, body mass index, comorbidities, AHI, ESS score) within one severity group.

4. Discussion

In a cohort of 141 patients with OSA, the vast majority did not exhibit central apneic events (CAEs) at all during REM sleep. This observation applies to mildly, moderately, and severely affected sleep apnea patients. In addition, when adjusted for the proportional sleep duration in REM and NREM sleep, the frequency of CAEs was significantly higher in

NREM sleep than in REM sleep only in the group of our severely affected OSA patients. This difference was not found in the mildly and moderately affected patients.

The study benefits from the use of a relatively large patient cohort. Of note, the groups of moderately and severely affected patients were very homogeneous regarding the distribution of epidemiological data. In contrast, the group of mildly affected patients presented a lower mean age and mean BMI, an issue that should be considered as a possible confounder. Data from all participants were recorded over two consecutive nights to minimize the first-night effect, and only the data from the second night were used for analysis [24]. The data were all recorded at the same sleep medicine center and were analyzed by a fixed group of experts according to current clinical AASM (American Academy of Sleep Medicine, Inc., Darien, IL, USA) standards. Since this was a retrospective study, the data for ESS, CVRF, or BMI were not available for some patients because they were not recorded at the initial consultation or later documentation (Table 1). Although the study is based on a retrospective data analysis, the data have been very well documented and reviewed.

To the best of our knowledge, we present in this report the first study describing the phenomenon of completely absent central apneas in REM sleep in a large group (and in a significant proportion) of OSA patients with varying disease severity. Previous studies that look at the associated OSA endotypes (e.g., increased loop gain) in the different sleep stages may have relevance to the occurrence of central events. However, as previously described, most such studies address differences in chemosensitivity between different sleep stages and preferentially include healthy subjects [10]. Reports that are also based on data from OSA patients are of particular interest for the interpretation of our results. We identified one study and one case report that met this condition, a study of 44 OSA patients used the loop gain metric to address the question of how the sensitivity of the ventilatory control system is altered by sleep stage [10,30]; loop gain was lower in REM sleep than in NREM sleep. Since central sleep apnea is associated with a high loop gain, the finding of Landry et al. [10] is, at least in part, consistent with our observation. However, we can confirm these results (when adjusted to the duration of the REM sleep phase) only for the group of severely affected OSA patients, for whom significantly more frequent CAEs could be detected in NREM sleep than in REM sleep. Within the cohorts of the mildly and moderately affected OSA patients, we found no statistically relevant difference between the frequency of CAEs in the REM and NREM sleep.

It should be noted that the studies show that loop gain is not excessively reduced in REM sleep, which is associated with an increase in plant gain [31]. This aspect should be taken into account when considering the differences between OSA severity levels. However, this requires standardized measurement methods and analyses and a large patient population to compensate for variations in physiological measurements [10,31].

Sensitivity of central and peripheral chemoreceptors is an important element in the control of respiratory drive. It has been shown (although mostly in healthy humans) that, as is the case for loop gain itself, chemosensitivity decreases from wakefulness to NREM sleep and is lowest in REM sleep [22,32]. It is assumed that the decrease in chemosensitivity has a protective effect against the occurrence of CAEs. On the other hand, it has been described that it may favor the occurrence of obstructive events (OS) [33], thus explaining the fact that OSA is often more severe during REM sleep. Since we found differences in the frequency of CAEs between REM and NREM sleep only in the group of severely affected OSA patients, one could conclude that a decrease in chemosensitivity and the reduction of loop gain (associated with an increased plant gain) could be responsible for this different frequency of CAEs in REM and NREM sleep.

These statements are in accordance with the observation that central apneas are more frequent in NREM sleep, which has been described before [12,22,34]. Nonetheless, to our knowledge, it has not yet been investigated how the frequency of CAEs relates to the different contributions of REM and NREM sleep to TST in OSA patients. The finding that the frequency of CAEs in relation to the duration of REM sleep differs only in the group of

severely affected OSA patients suggests that the pathophysiology of the development of CAEs in OSA patients should be considered differently from the development of CAEs in cohorts of variable OSA severity and of course in cohorts of healthy individuals or cohorts of patients with central sleep apnea.

The Pre-Boetzinger complex (PreBoetC), being one of the four cell groups of the ventral respiratory group (VRG), is the main site of neuronal rhythmic respiratory pattern generation [35–37]. In animal models, cells of the PreBoetC were selectively destroyed, resulting in central apneas during sleep [38]. These CAEs occurred initially in REM sleep and, after some time, also in NREM sleep and during wakefulness. The authors concluded that the age-related increase in prevalence of sleep-related breathing disorders may indicate a neurodegenerative background of these disorders. In addition, other authors have found a correlation between age and the frequency of CAEs and offer explanations for it [39]. However, within each OSA severity group, we did not find any significant correlation between the age of the patients and the occurrence or persistence of central apneic events. This means that within a group, i.e., within the group of severely affected OSA patients, no correlation between the age of the individual patient and the prevalence of central apneic events could be proven. Thus, the statistical analysis was performed within a patient group and not between patient groups. For in terms of AHI, obstructive sleep apnea is undoubtedly a disease associated with the aging process and in our data, we were able to find differences in the mean age of the three groups (mildly, moderately, and severely affected) that support this relationship.

From another perspective, REM-sleep-associated neuronal circuits beyond the brain- stem that are connected to the PreBoetC or other VRG sites in humans may act protectively against the emergence of CAEs during REM. Given that emergence of CAEs is strongly as- sociated with the chemosensitivity of the brainstem nuclei regulating breathing mechanics, our results may provide insight into the relationship between decreased chemosensitivity of brainstem nuclei and the severity of OSA [22,37].

The adjustment of CAE frequency to the duration of the REM sleep phase, as per- formed in the present report, should be considered critically: CAEs are in general rare and occur in very low frequency during REM sleep. In order to compare the absolute values of CAEs in REM and NREM sleep (with their different contributions to TST), the duration of REM sleep was chosen as a reference because it allows for a better depiction of the original data, i.e., the original number of CAEs occurring in REM sleep. The duration of NREM sleep (and thus the number of CAEs) is mathematically reduced with the normalization performed, resulting in lower values of CAEs in NREM sleep. Alternatively, it would have been possible to normalize the duration of REM sleep to the duration of NREM sleep or TST, but this would have led to very high numbers of CAEs in REM sleep, which we do not consider physiologically realistic. Therefore, the observation of rarely occurring CAEs is statistically very ambitious and we hence recommend for future studies on this topic to use even greater patient cohorts than the present one. Likewise, we point out that the analysis regarding the number of central apneic events in REM and NREM was not performed between the groups but only within one patient group. We chose this procedure because it is clear from the sleep parameters that the groups cannot be compared with each other, especially when regarding the comparison of a rarely occurring phenomenon (namely, central apneic events) in relatively short parts of the TST (i.e., REM sleep). The REM sleep duration is so short that it is physiologically impossible to detect a sufficient number of CAEs in one or two PSG nights to be able to calculate meaningful statistics, which we consider as the main limitation of our study. On the basis of our data, we predict that it would take more than five PSG nights to be able to collect sufficient data points. This fact should also be considered for all previously published work in the field to date, but also for future studies. The feasibility of such an approach is, of course, questionable. Nevertheless, we would like to explicitly showcase this quite relevant problem. In addition, these data sets should be used to calculate the loop gain at the different sleep stages and correlate the results with the observations.

To gain further insight into the relationship between the severity of OSA and the occurrence of central apneas during the different sleep phases, prospective studies including pCO_2 measurements (capnography) during PSG would be of paramount importance. In addition, a parallel consideration of the patients' cortical arousal profile may provide additional information, given that cortical arousals not only are strongly associated with the severity of respiratory distress in OSA [35] but may also lead to hypocapnia via arousal- related increased chemosensitivity patterns, which may suppress the respiratory drive in OSA patients [40–43].

5. Conclusions

In summary, we demonstrated, apart from the known fact that central apneas are less frequent during REM sleep than during NREM sleep in OSA patients, that a great majority of OSA patients do not have any central apneas at all during REM. In addition, we provide novel evidence that when adjusted to the respective REM sleep duration, an increased number of CAEs in NREM (compared to REM) sleep is found only in the group of patients severely affected by OSA. This difference could not be found in the mildly and moderately affected patients. The pathophysiological mechanisms are unknown so far, but our findings support a correlation between chemosensitivity and OSA severity. Further studies are needed to investigate the relationship between these parameters in more detail.

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3 Diskussion

„Machine Learning“ (ML) ist ein Teilgebiet der Statistik. Mithilfe dieser Methode werden algorithmische Modelle trainiert, um Klassifizierungen oder Vorhersagen zu treffen und in „data-Mining“-Projekten wichtige Erkenntnisse zu gewinnen (33). Für das Paper „A Novel Quantitative Arousal-Associated EEG- Metric to Predict Severity of Respiratory Distress in Obstructive Sleep Apnea Patients“ wurde sich bewusst für eine Methode aus dem Bereich des machine learning entschieden, um wie im oben genannten, die Genauigkeit von Vorhersagen zu verbessern. Dabei ist die support vector machine (SVM), welches als zentrale Aufgabe die Klassifizierung von Daten hat, ausgewählt worden. Anhand vorhandener Daten und Datenzuordnungen ist über die Klassifizierung zu entscheiden, welcher Klasse ein neues Datenobjekt zugeordnet werden kann. Dabei muss vorerst die SVM mit einer Datenbasis „trainieren“, deren Klassenzuordnung bekannt ist. Danach werden mithilfe von Trennlinien und Trennflächen versucht neue Objekte den richtigen Klassen zuzuordnen. Bei realen Problemstellungen sind Klassen häufig nur von nicht linearen Trennlinien zu klassifizieren, was bei der SVM über Erweiterung der Dimensionen (Hyperebenen) des Trennungsvektors erreicht wird. Für die Hoch- und Rücktransformation dieser Ebenen, wird die Kernelfunktion zur Beschreibung der Trennflächen benutzt (34). Wie dabei dem Paper zu entnehmen ist, konnte man mit Hilfe der SVM und der neuen arousal- AUC metric eine sehr gute Vorraussagekraft für den AHI, hypoxic burden und den arousal index abbilden. Auch andere Arbeitsgruppen konnten schon positive Beweise dafür liefern, dass die Methoden des machine learning ein aussagekräftiges Tool, in der Diagnostik der OSA sein können (35-37). Ein systematisches Review von Bazoukis et al (38) konnte insgesamt 132 Studien finden, die sich mit einer Implementierung von ML im Bereich der Diagnostik, Vorhersagekraft des Schweregrades oder Therapie Optimierung von OSA beschäftigten. Dabei wurde konstatiert, dass ML-Techniken eine entscheidende Rolle bei der Diagnose und Behandlung von Schlafapnoe spielen könnten. Doch auch trotz dieser positiven Studienbeweise, ist eine Implementierung von machine learning in den klinischen Alltag eine große Hürde. Um im Bereich der Schlafmedizin zu bleiben: Trotz einem großen Angebot an AI-Software für das automated Sleep scoring nach der PSG, wird durch die AASM weiterhin der Goldstandard in einer menschlich kontrollierten Auswertung gesehen. Die Gründe für die Schwierigkeiten zur Implementierung sind divers. Zum einen sind die Ergebnisse der AI-Software abhängig von der Qualität der Daten, mit welchen sie trainiert wurden. Dabei gibt es zurzeit keine Reglementierung, was für Datensets verwendet werden müssen. Somit bleibt es offen, wie viele Patienten für die Rekrutierung der Daten implementiert wurden. Die meistgenutzten Datensets stammen aus regionalen Studien (z.B. Montreal archive of sleep studies, Wisconsin sleep cohort, sleep heart health study, Massachusetts General Hospital sleep laboratory). Diese unterscheiden sich häufig im Alter und Anzahl der Teilnehmer bzw. Patienten und im Krankheitszustand dieser (siehe Abb.2).

Datensets	Alter	Anzahl der Teilnehmer	Krankheitszustand
EDF-Sleep	25-101	197	gesund
Montreal archive of sleep studies	18-76	200	gesund
MGH sleep laboratory	18-93	1985	gesund & OSA
Sleep heart health study	39-90	5804	gesund & OSA
CAP sleep	14-82	108	gesund oder versch. Schlafstörungen
ISRUC sleep	20-85	118	gesund & OSA
Wisconsin sleep cohort	37-85	2570	Gesellschaftsstichprobe
MIT-BIH database	32-56	16	COPD

Abbildung 2: AASM - What the Sleep Fellow Needs to Know about Artificial Intelligence 9. März 2022, (39).

Um bessere Trainingsdaten zu generieren, müssten überregionale Datenbanken erstellt werden. Dies ist im heutigen Gesundheitswesen jedoch schwierig, da es diverse Systeme zur Speicherung von Gesundheitsdaten gibt. Diese unterscheiden sich schon innerhalb Deutschlands und sind meist ohne die Einrichtung von Schnittstellen nicht kompatibel. In der freien Wirtschaft investieren aufstrebende Unternehmen viel Geld, um mit Hilfe von menschlichen Experten, Daten in das richtige Format zu transferieren und dann in Datenbanken zu implementieren. Ebenfalls ist der sichere Umgang mit solch sensiblen Daten eine große Herausforderung. Nichtsdestotrotz zeigen die oben gelisteten Studien, dass aus der Nutzung künstlicher Intelligenz eine bessere medizinische Versorgung entstehen könnte, sodass es die aufgezeigten Probleme zu überwinden gilt.

4 Zusammenfassung

In der Publikation “A Novel Quantitative Arousal-Associated EEG-Metric to Predict Severity of Respiratory Distress in Obstructive Sleep Apnea Patients” konnte gezeigt werden, dass durch die Anwendung von Maschine Learning, ganz spezifisch, der support Vektor Regression und einem möglichen neuen Parameter, der „area under the curve of respiratory arousal“, eine sehr hohe Voraussagewahrscheinlichkeit für den AHI, hypoxic burden und arousal index geschaffen werden konnte. Daher könnte dieser neue Parameter als zusätzlicher, quantitativer und stellvertretender Marker zur weiteren Beschreibung des Schweregrades von OSA genutzt werden. Weiter spricht dieser Befund dafür, dass nicht nur allein die Intensität (maximaler Ausschlag) oder die Gesamtlänge eines Arousal, sondern die gesamte Mikrostruktur, relevant für den Schweregrad und damit die Belastung der Erkrankung sind. Solch eine komplexe und feine Auswertung der Polysomnographie, um auch die Mikrostruktur von Kurven miteinzubeziehen, ist manuell kaum möglich. Daher ist in Zukunft die Anwendung von maschinellem Lernen, wie in dieser Publikation demonstriert, ein weiterer Schritt, zur genaueren Differenzierung von Pateinten mit obstruktiver Schlafapnoe. Mit der Publikation “Central Apneic Event Prevalence in REM and NREM Sleep in OSA Patients: A Retrospective, Exploratory Study” wurde Anschluss an die Datenauswertung des Datenpools der vorausgegangenen Studie genommen. Auffallend war, dass ein Großteil der Probanden keine zentrale Schlafapnoe während der REM-Schlafphase aufzeigte, was bisher in der uns bekannten Literatur nicht beschrieben worden ist. Weiter war unter Berücksichtigung der proportionalen Schlafdauer im REM- und NREM-Schlaf, die Häufigkeit von CAEs, nur in der Gruppe der schwer betroffenen OSA-Patienten, im NREM-Schlaf signifikant höher als im REM-Schlaf. Dieser Unterschied konnte nicht in der Gruppe der mild oder moderat betroffenen Probanden gefunden werden. Das könnte ein Hinweis auf die unterschiedliche, pathophysiologische Entstehung von CAE in verschiedenen Schweregraden von OSA-Probanden, wie auch im Unterschied zur gesunden Bevölkerung sein. Die Daten bestärken die bestehende Annahme, dass ein Zusammenhang zwischen der Chemosensitivität der Hirnstamm Nuclei und dem Schweregrad von OSA besteht. Um weitere Erkenntnisse zu erlangen, sind jedoch Folgestudien nötig.

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6 Tabellarischer Lebenslauf