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PILOT STUDY

CORRELATION BETWEEN DESATURATION INDICES OF OXYGEN SATURATION VARIABILITY IN SEVERE OBSTRUCTIVE SLEEP APNEA: A PILOT STUDY

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Background: Obstructive sleep apnea (OSA) is a respiratory disorder characterized by recurrent airflow obstruction caused by total or partial collapse of the upper airway**.** The aim of this study is to compare the accuracy of the different indices derived from pulse oximetry (SpO_2V) using free software in the diagnosis of severe OSA and to determine the relationship of these indices with the apnea-hypopnea index (AHI), cumulative time spent below 90% SpO_2 (T90) and the oxygen desaturation event index (ODI). **Methods:** Cross-sectional study with 20 untreated severe OSA patients AHI>30 and 11 subjects with AHI<5 referred to a sleep laboratory. The AHI, T90 and ODI indices were calculated from pulse oximetry simultaneously during polysomnography. To analyze SpO_2V, interval of oxygen pulse wave (IOP) index, standard deviation of IOP (STDIOP), mean of oxygen saturation (MOS), root mean square of IOP standard deviation (SDIOP) of SpO_2V were calculated. **Results:** OSA subjects presented with higher values of IOP, STDIOP, SDIOP when compared to controls (P<0.05). T90 demonstrated a positive correlation with IOP (r 0.94), STDIOP (r 0.64) and SDIOP (r 0.73) as well as ODI with IOP (r 0.79), STDIOP(r 0.78), SDIOP (r 0.73) and AHI with STDIOP (r 0.76), SDIOP (r 0.73). The area under the ROC curve of IOP, STDIOP, SDIOP were 0.93, 0.99, and 0.99, respectively. **Conclusions:** SpO_2V was correlated with AHI, ODI and T90 indices and presented positive predictive value for OSA. The SpO_2V could be useful and allows for a non-invasive widely applicable diagnostic technique for severe OSA.

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INTRODUCTON

Obstructive sleep apnea (OSA) is a respiratory disorder characterized by recurrent airflow obstruction caused by total or partial collapse of the upper airway[1-3]. Epidemiological studies have shown a 33% prevalence of OSA among individuals between 50-70 years of age[2,4]. The most common symptoms of OSA patients include chronic loud snoring, excessive daytime sleepiness[5], personality changes[6] and deterioration of quality of life[7]. Apnea episodes are accompanied by hypoxemia and terminate with micro arousals, resulting in sleep fragmentation[3,4]. The repetitive hypoxia and subsequent reoxygenation phenomena may cause oxidative stress and contribute to increased risk for cardiovascular disease[8,9]. In this way, nocturnal desaturation constitutes one of the most relevant consequences of OSA, contributing to an increased risk for arrhythmias and sudden death. Lastly, OSA is associated with marked cardiovascular morbidity and mortality[10,11,]. Nocturnal pulse oximetry is currently a popular American Academy of Sleep Medicine type 4 monitoring technique used to screen OSA[12], due to, among other things, its low cost. For instance, overnight oxygen saturation monitoring is a widely accepted screening tool in the diagnosis of OSA and has been used to classify severity[13]. Several studies have analyzed nocturnal pulse oximetry from different perspectives: visual scoring[14], oxygen desaturation index (ODI)[15] and cumulative time spent with peripheral oxygen saturation (SpO2) below 90% (T90)[16]. However, these indices lack sufficient sensitivity and specificity and therefore have not gained widespread clinical acceptance as a definitive screen for OSA.

The time domain indices[17], as well as mathematical models[18], provide automatic scoring which improve sensitivity and specificity[17,18]. However, sophisticated algorithms are difficult and rarely applied in clinical practice. These reasons led the authors to conceive and propose a novel methodology which they believe may prove useful for the diagnosis of OSA. According to this approach, the SpO_2 variability (SpO_2V) signal is derived by considering subsequent SpO_2 intervals (SpO_2i) between successive SpO_2 pulse wave values. The SpO_2V is subsequently analyzed by a software package traditionally used for heart rate variability analysis.

Our objective, therefore, was to investigate whether the hereby proposed method for SpO_2V analysis is reliable for OSA screening. Secondly we comprehensively evaluated the ability and reliability of the representative proposed indices in the time domain obtained in the free software and correlated these findings with ODI, AHI and T90 indices. The hypotheses of this study are that: 1) the proposed indices are highly sensitive and specific for the diagnosis of severe OSA. 2) there are relationships between SpO_2V indices and AHI, ODI and T90 indices.

MATERIALS AND METHODS

Subjects

We studied overnight polysomnographies of untreated patients with severe OSA (OSA Group) and subjects with apnea/hypopnea index (AHI) <5 (Control Group) referred to sleep laboratory (Instituto do Sono of São Carlos, São Paulo, Brazil). Exclusion criteria included permanent or paroxysmal atrial fibrillation, permanent ventricular or atrial pacing, current tobacco use, pulmonary and neurological disease, periodic legs movements and participation in trials with continuous positive airway pressure devices in the previous six months.

The study protocol was approved by the local Ethics Review Committee (401/2010) and all participants signed written informed consent forms.

Study Design

The present study is a cross-sectional investigation. All subjects provided written informed consent to participate in the study. All subjects simultaneously underwent nocturnal polysomnography (PSG) and an overnight recording of oxygen saturation by SpO_2, between February and July 2010. A clinical evaluation and Epworth Sleepiness scale were performed before the analysis.

Polysomnography

The nocturnal polysomnography (Icelera Fast-Poli 26i, 2008, Homed, Brazil) included the monitoring of electroencephalogram, electro-oculogram, oronasal flow by thermistor, transducer nasal pressure, thoracoabdominal movement, electrocardiogram, snoring and body position[19]. The polysomnogram was scored manually according to standard criteria by an experienced evaluator blinded to other study data.

According to the parameters established by the Task Force of AASM [20] , apnea was defined as the absence of airflow for more than 10 s, and hypopnea as the reduction of respiratory flow for at least 10 s accompanied by a 3% or greater decrease in the saturation of hemoglobin. Severe OSA was defined as an apnea/hypopnea index (AHI) >30 per hour, and normal as an AHI < 5 per hour[21]. The AHI was calculated by dividing the number of apneas and hypopneas by the number of hours of sleep[22]. Each episode of apnea was characterized by measuring apnea duration and mean and minimal arterial oxyhemoglobin saturation. Total sleep time, number and duration of REM periods, and number and duration of arousals were also measured[23].

Overnight Nocturnal Pulse Oximetry

Overnight nocturnal SpO_2 (Ox-p-10, Emai, Brazil), was measured during the sleep study using a Linger probe with a sampling frequency of 1.0 Hz. The data WERE digitally stored in the pulse oximeter. .

The SpO_2 signal was analyzed and the following indices were calculated: minimal SpO_2, mean SpO_2, defined as the cumulative time spent with SpO_2 below 90%. The oxygen desaturation event index (ODI) was defined as the number of events per hour in which oxygen saturation decreases by 4% or more from baseline. Baseline was set initially as the mean level in the first 3 min of recording.

SpO_2V was obtained by the variability of SpO_2 in each pulse wave. After polysomnography was scored, we separated the SpO_2 signal according to all sleep stages (S2, S3, REM) as well as merged all overnight data. The SpO_2 stage and cumulative data were saved to separate files and processed off-line by Kubios HRV Analysis software (MATLAB, version 2 beta, Kuopio, Finland).[24]

The time-domain methods were applied straight to the series of successive SpO_2 interval (SpO_2i) values, acquired at a sampling rate of 1 Hz We calculated the interval of the oxygen pulse wave according to formula (1):

$$SDIOP = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N-1}(SpO2i + 1 - SpO2i)^2} \qquad (1)$$

where SDIOP is the IOP standard deviation and N is the sample number.

Statistical Analysis

After verifying normal distribution with Kolmogorov-Smirnov test, data of the patients were reported using mean values and SDs. Inter-group differences were evaluated by parametric unpaired t-tests.

Sensitivity and Specificity of SpO_2V for Screening in OSA: Nocturnal SpO_2 was used as the test and polysomnography as the gold standard for the correct classification of OSA patients. A receiver operating characteristic (ROC) curve was constructed, representing the comparative course of sensitivity and 1-specificity (1 minus the specificity expressed as a decimal) at different thresholds.

The Pearson Correlation test was used for comparison between SpO_2V and OSA severity indices. A p-value smaller than 0.05 was considered significant for all tests. The analysis was performed with MedCalc statistical software, Version 11.4.4.0 (MedCalc Software, Mariakerke, Belgium) and Sigma Plot version 11.0 (Systat Software, Germany).

RESULTS

We evaluated 65 polysomnographies with diagnostic of severe OSA (AHI> 30), and 23 with non-OSA diagnostic (AHI<5), with 45 OSA patients and 12 non-OSA subjects being excluded because of of poor technical quality due to interferences or movements and artifacts mimicking oxygen desaturation. Twenty untreated severe OSA patients and eleven normal subjects were included in this analysis. Baseline anthropometric, sleep parameters, and comorbidity characteristics are presented in Table 1. No statistically significant differences were observed in the height and age values between the groups (p=0.51 and p: 0.74). Patients with severe OSA presented with significantly greater weight and BMI values compared to the control group (p=0.005). The Epworth Scale score was higher in the OSA group compared to the control group, 19% in OSA group and 30% in control group were ex-smokers.

As expected, a significant greater value was observed in AHI, Arousal index, Apnea/hours of sleep and hypopnea/ hours for sleep in patients with OSA. Compared to the control group, no significant differences were found in sleep efficiency, sleep total latency, stage REM latency and total sleep time. No study participants had technical problems performing the PSG and overnight oximetry (Table 1).

ODI, T90, and total oxygen desaturation were higher in OSA group when compared with controls. In addition, compared to controls, the OSA group presented lower SpO_2 and minimal SpO_2 (Table 2). In the time domain analysis, the IOP, STDIOP, SDIOP were higher in OSA patients in the overnight analysis as well as all individual sleep stages (table 3).

The ability of IOP, STDIOP, and SDIOP to discriminate between patients with and without OSA according to the polysomnography gold standard is listed in Table 4.

The area under the ROC curves showed that IOP, STDIOP and SDIOP presented a very favorable level of sensitivity and specificity. .

Table 1: Demographic, anthropometric, clinical and polysomnographic parameters in Control Group and OSA Group

	Control Group (N=11)	OSA Group (N=20)	p-Value
***Age* (*years*)**	49±11	49± 13	0.051
Males (%)	7 (80)	17 (85)	0.209
Weight (kg)	72±11	93±12	<0.001
Height (cm)	170± 8	174±6	P>0.05
BMI(Kg/m	25± 3	31± 4	0.0005
Ex-smokers (%)	3 (30)	3 (15)	0.6381
Epworth Sleepiness Scale	6±2	10±3	
AHI (events/h)	2.8±1.1	48 ±18.2	< 0.0001
Arousal index (events/h)	6.7± 2.6	23.2 ±18	0.0014
Apnea/hour of sleep	0.65±0.5	32.8±23.8	0.0006
Hypopnea/hour of sleep	2.1±1.0	17.6±10.0	< 0.0001
Sleep efficiency (%)	86±9	80 ±15	0.2585
Sleep total latency (min)	12±13	19±15	0.2801
Stage REM latency (min)	18±15	142±69	0.3202
total sleep time(min)	6.1±0.9	6.0±1.3	0.4301

Quantitative data are expressed by mean ± SD. OSA: Obstructive Sleep Apnea; BMI: Body Mass Index; AHI: Apnea/ Hipopnea Index; REM: rapid eyes movement.

Table 2: Oxygen parameters of Control Group and OSA Group during overnight polysomnography

	Control Group (N=11)	OSA Group (N=20)	p-Value
ODI (4% level)	11.4± 18.4	63.5±30.6	< 0.0001
T90 (min)	0.14±0.2	100.5 ±95.0	0.003
Basal saturation %	96.3±1	95.1±1	0.037
Average oxygen saturation (%)	94 ±0.7	90.5 ±2.5	0.0004
Minimal oxygen saturation (%)	89±1	75±10	0.0002
Total oxygen desaturation (n)	29±17	333±175	< 0.0001

Quantitative data are expressed by mean **±** SD. ODI: Oxygen Desaturation index; T90: Cumulative time spent below 90% saturation

Table 3: SpO_2V in Control Group and OSA Group separate stages of sleep define S2 and S3 in this table

	SpO		SpO		SpO	
	Control Group (N=11)	**OSA Group (N=20)**	**Control Group (N=11)**	**OSA Group (N=20)**	**Control Group (N=11)**	**OSA Group (N=20)**
IOP(ms)	635.7±4.2	658.2±14.4 ǂ	635.7±4.2	658.0±15.1 ǂ	633.9±6.1	670.3±38.7 ǂ
STDIOP(ms)	2.4±0.3	7.5±3.0 ǂ	2.4±0.3	5.2±3.2*	2.9±0.6	10.6±11.2*
SDIOP(ms)	1.5±0.2	3.1±0.7 ǂ	1.5±0.2	2.5±0.9 ǂ	1.7±0.2	3.7±1.7 ǂ

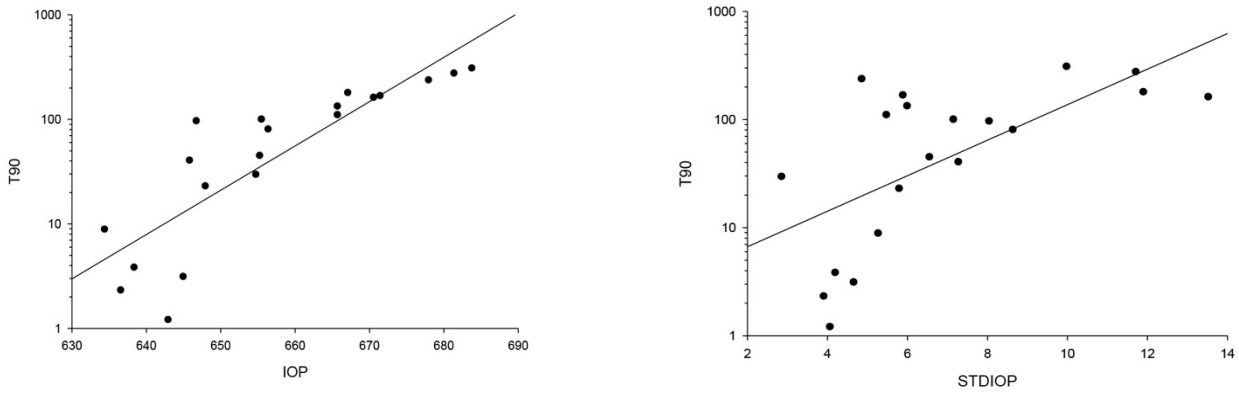
Quantitative data are expressed by mean **±** SD. IOP: interval of oxygen pulse wave; interval of oxygen pulse wave; STDIOP: standard deviation of IOP; SDIOP: root mean square of IOP standard deviation; * $p<0.05$; **ǂ** $p<0.001$.

Table 4: Accuracy of the indices derived of SpO_2V in the diagnosis of OSA

Index	**cutoff**	**AROC**	**Se %**	**Sp%**
IOP (ms)	641	0.93 (0.77 to 0.98)	85	100
STDIOP (ms)	3.03	0.99 (0.88 to 1.0)	95	100
SDIOP (ms)	1.85	0.99 (0.88 to 1.0)	95	100

IOP: interval of oxygen pulse wave; interval of oxygen pulse wave; STDIOP: standard deviation of IOP; SDIOP: root mean square of IOP standard deviation. Se: sensitivity; Sp: specificity; AROC: area under ROC curve.

Figure 1 shows the relationship between T90, ODI and AHI with the indices derived from the time domain analysis of overnight SpO_2V in OSA patients. T90 demonstrated a significant positive correlation with IOP, STDIOP, and SDIOP (A, B, C), as well as ODI with IOP, STDIOP, and SDIOP (D, E, F) and AHI with STDIOP and SDIOP (G, H).



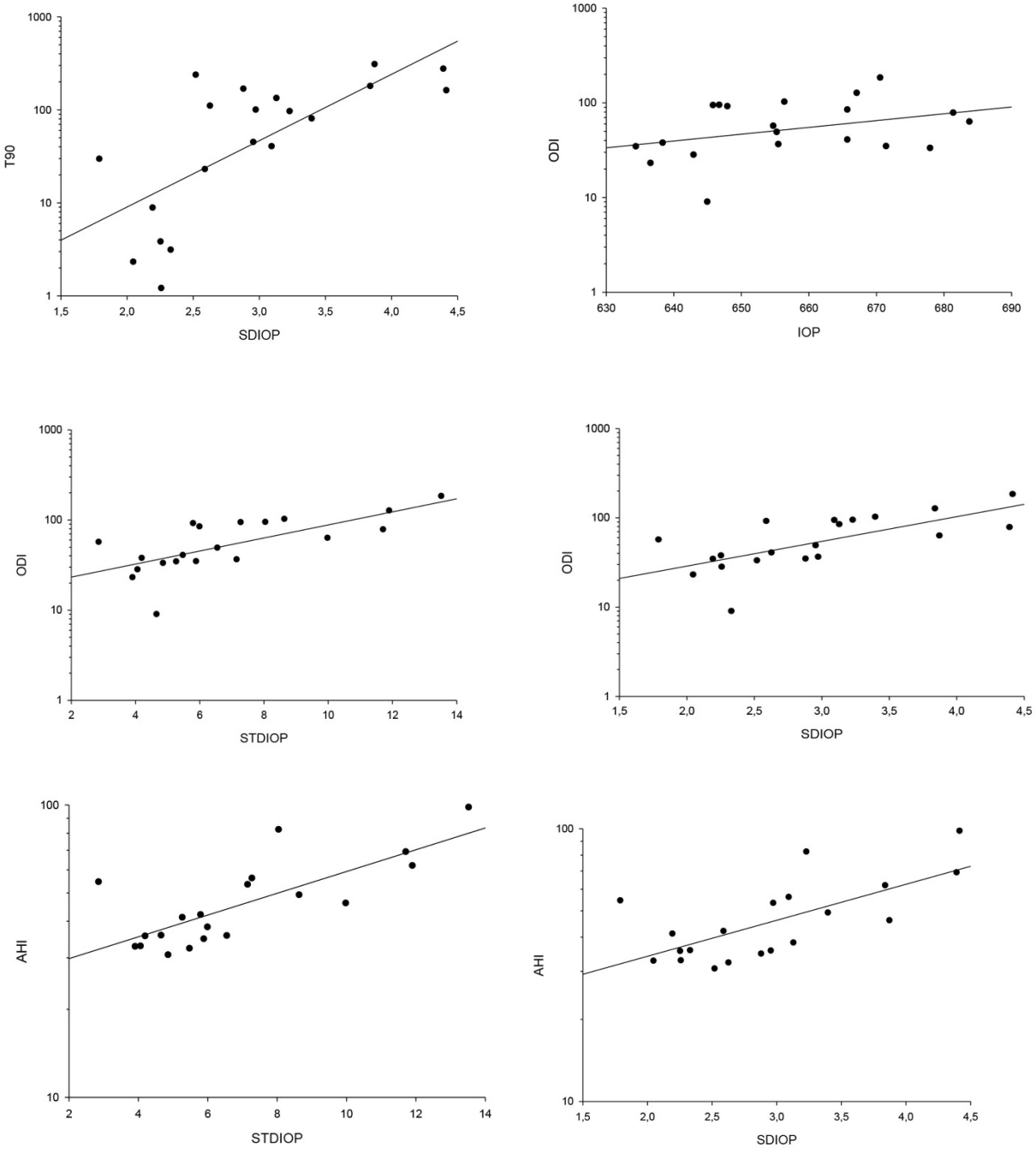


Figure 1: The correlation between T90 and IOP (A), STDIOP (B), SDIOP (C). Correlation between ODI and IOP (D), STDIOP (E) and SDIOP (F). Correlation between AHI and STDIOP (F) and SDIOP (G). IOP: interval of oxygen pulse wave; interval of oxygen pulse wave; STDIOP: standard deviation of IOP; SDIOP: root mean square of IOP standard deviation; T90: Cumulative time spent below 90% saturation; ODI: Oxygen Desaturation index; AHI: apnea/hypopnea index.

DISCUSSION

The most important finding of the present study was that the recurrence of apnea events in patients with OSA coincided with a significant increase in SpO_2V with higher time domain parameters values.. In OSA patients, oxygen desaturations associated with apnea events cause fluctuations in the SpO_2 signal leading to high SpO_2V values.

In this context, high SpO_2V may indicate the presence of OSA and could provide useful, additional information for diagnosis formulation.

We demonstrated that patients with severe OSA in the present study had a higher BMI when compared to matched controls, however these patients did not have obesity hypoventilation syndrome (OHS) characteristics. OHS is defined by the triad of obesity, daytime hypoventilation, and sleep-disordered breathing without an alternative neuromuscular, mechanical, or metabolic cause of hypoventilation [25]. Our results are in agreement with Pinto et al[25] and TuLik et al[4], who showed that BMI was significantly related with the AHI index, an important indicator of OSA severity.

As expected, ODI and T90 indices demonstrated significantly higher values in OSA patients, which confirmed a substantial oxygen desaturation. The minimal oxygen saturation was lower and total desaturation was greater in the OSA group. When comparing our results with previous studies on pulse oximetry[12,] we can confirm that OSA patients had significantly higher SpO_2V obtained by the nocturnal pulse signal, indicating that OSA patients demonstrate greater SpO_2 irregularity compared to non-OSA patients. Our results were supported by a recent study by Del Campo et al[26], which showed desaturation was associated with OSA severity. In the present study, we used time domain analysis of the SpO_2 pulse wave throughout the sleeping period. When we analyzed the parameters of SpO_2V separately, in all stages of sleep, the indices derived in the time domain and frequency domain are indicative of high variability signals in OSA patients. In this context, fluctuations in the time domain may reveal significant information on the dynamic characteristics lost with routine averaging or linear methods[2].

Moreover, the time domain indices proposed in our study (IOP, STDIOP and SDIOP) presented a strong positive correlation with known indices used routinely in sleep studies[13]. It is well known that AHI is related to morbidity and mortality in OSA patients[10]. In addition, desaturation in such individuals may be more predictive of cardiovascular outcomes compared to the predictive ability of the number of awakenings. Rahangdale et al[16] showed that desaturation time was predictive of platelet activation. Moreover, both ODI and T90 reflect desaturation but may differentially indicate important physiological variations in subjects with OSA and desaturation indices may allow us to predict platelet activation and other sequelae of OSA. Thus, the proposed indices in the present study may be interesting since they constitute a simple tool in a free software package.

There are a number of studies[2,12,13,15,17] that have evaluated the use of pulse oximetry with the hope of simplifying the screening of OSA while preserving a high level of diagnostic accuracy. The central question of these investigations is: can overnight pulse oximetry be used as a surrogate for polysomnography? Sensitivity of overnight pulse oximetry for at least moderately severe OSA can be higher, however, the specificity can be lower, depending on how the data are interpreted[17]. Levy et al[27], using a mathematical index to detect changes in SpO_2, found a sensitivity of 90% and a specificity of 75%, utilizing a 12-s sampling frequency allowing for reasonable resolution of SpO_2 variability (Δ index). This index corresponds to the sum of the absolute variations between two successive points, divided by the number of intervals. However, the specificity of of the proposed index was low despite good sensitivity. Zamarrón and colleagues[28-30] assessed several mathematical models with data derived from digitized pulse oximetry to analyze the variability of saturation and, through complex algorithms, demonstrated satisfactory sensitivity and specificity. Recently, Poupard[18] proposed a new mathematical analysis from wavelet-aggregate using the relationship between Δ SpO_2 and ΔHR for OSA screening, reinforcing the importance of studies to investigate the behavior of oxygen saturation as a diagnostic tool in this population. However, all the aforementioned studies used complex mathematical models that are not readily applicable in clinical practice. In the present study we used the same algorithms that have been previously applied to Heart Rate Variability (HRV) analysis, which is more clinically applicable while preserving diagnostic accuracy.

In our study, the ROC curves parameters of SpO_2V derived from the analysis of time domain presented with high sensitivity and specificity for the identification of patients with severe OSA, compared to conventional polysomnography as the gold standard. Our results suggest that, as a diagnostic test, the analysis of SpO_2 variability provides good sensitivity and specificity compared to

traditional methods. The time domain indices showed that IOP had a sensitivity of 85% and specificity of 100%, STDIOP had sensitivity of 95% and specificity of 100%, and SDIOP had sensitivity of 95% and specificity of 100%.

On the other hand, the spectral analysis and time domain analysis have an inherent mathematical complexity. From the point of view of clinical use, this complexity is completely overcome when user-friendly software is used to derive these calculations. We utilized the Kubios software package that was developed for heart rate analysis. We think this could be a complementary method to the conventional indices calculation, that could be introduced in the same system without any additional costs.

Limitations

There are always some technical and physiological limitations associated with overnight pulse oximetry for diagnosing OSA. The poor contact between the probe and the finger due to body movements and bad regional circulation occasionally produces signals presenting multiple decreases in SpO_2. However, we examined our recordings before the analysis with visual inspection to indentify evidence of technical problems and all data sections that registered drops to zero were discarded. Such visual inspection is fundamental to guarantee good signal quality.

Another limitation was that we only included subjects with a diagnosis of severe OSA or who did not have this condition. We did not analyze patients with mild-moderate OSA severity. The selected severe OSA threshold for the subjects may have affected the sensitivity and specificity results, but our study has clinical importance for reducing cardiovascular risk in this population since cheap and fast diagnosis may encourage strategies for the treatment.

Therefore, the applicability of our findings to patients with OSA in the mild-moderate range may be limited. In this context, a large population with different grades of severity is required in future studies to test the potential value of our methodology. Further research to prospectively assess the accuracy of our methodology, enlarging the data set and considering a wider spectrum of sleep-related breathing is needed.

CONCLUSIONS

We conclude that the analysis of SpO_2V recorded by overnight pulse oximetry provides parameters which positively correlate with AHI, ODI and T90 indices; the obtained SpO_2V indices were able to discriminate severe OSA patients with a high degree of diagnostic accuracy. Thus, SpO_2V analysis could represent a non-invasive and widely applicable diagnostic technique for patients with severe OSA.

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