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Experimental Research Article

Impaired respiratory control system adaptability in patients with COPD: Evidence from complexity analysis of oxygen saturation variability

Fatemeh Abbasi Feijani[1], Saeed Hajihashemi[1], Abdollatif Moini[2], Saeed Pazhoohan[1*]

1. Department of Physiology, Faculty of Medicine, Arak University of Medical Sciences, Arak, Iran
2. Department of Internal Medicine, Amiralmomenin Hospital, Arak University of Medical Sciences, Arak, Iran

ABSTRACT

Introduction: People with chronic obstructive pulmonary disease (COPD) often experience exacerbations and impaired gas exchange, leading to hypoxemia that may require hospitalization. Pattern analysis of capillary oxygen saturation (SpO2) variability can provide valuable insight into the adaptive capacity of the respiratory control system under this condition. Therefore, this study tested the hypothesis that the adaptability of the respiratory control system is reduced in patients with COPD.

Methods: In this study, we utilized entropy and fractal-like correlation properties of SpO2 time series in patients with COPD. We analyzed pulse oximetry data from 13 patients with COPD during hospitalization and discharge time and compared them to 16 age- and sex-matched control subjects. SpO2 variability analysis of a 25-minute time series was performed using sample entropy, multiscale entropy, and detrended fluctuation analysis.

Results: Entropy analysis revealed a complex pattern of SpO2 variability in healthy controls and patients with COPD. Both short-term (α1) and long-term fractal-like exponent (α2) were higher in patients with COPD compared to healthy controls. SpO2 entropy and mean were significantly lower in patients with COPD in comparison with controls. There was no statistically significant difference in SpO2 complexity measures between the hospitalization and discharge phases in these patients.

Conclusion: The respiratory control system in patients with COPD exhibits less complexity and information processing. These non-invasive analytical methods have the potential for future clinical application to monitor the integrity of respiratory control in individuals suffering from chronic respiratory diseases.

Keywords:
Oxygen saturation variability
Pulse oximetry
Entropy
COPD
Hypoxia

Introduction

Chronic obstructive pulmonary disease (COPD) affects more than 300 million individuals and is the third leading cause of mortality globally, causing 3.23 million deaths in 2019 (Adeloye et al., 2022; WHO Accessed

* Corresponding author: Saeed Pazhoohan, s.pazhoohan@arakmu.ac.ir
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16 March 2023). Patients with COPD often experience exacerbations, which require frequent hospital readmissions (Al Rajeh et al., 2021). COPD is usually considered a progressive disease and the ultimate damage to different components of the respiratory system can result in the development of hypercapnia and hypoxemia (Fleetham et al., 1980; Kent et al., 2011).

The pulse oximeter is a widely used non-invasive monitoring technique in medical practice. It is utilized for estimating blood oxygen saturation (SpO2) and assisting in the detection of hypoxemia (Jubran 2015). Nonetheless, depending solely on the absolute or mean SpO2 value may inadequately reflect the integrity of the respiratory control system (Amalakanti and Pentakota 2016; Costello et al., 2020; Jiang et al., 2021).

Recently, studies have shown that the SpO2 time series exhibit a complex pattern of fluctuations. It has been proposed that the analysis of SpO2 variability may provide valuable information about the integrity of the cardiopulmonary control system, which plays a crucial role in body oxygenation (Bhogal and Mani 2017). There are methods for quantification of the pattern and complexity of fluctuations in physiological time series. For example, sample entropy is a well-established tool used that measures the irregularity in a given time series with the ability to quantify information processing in a control system (Costa et al., 2005; Richman and Moorman 2000). A lower value of sample entropy indicates a higher level of regularity in the physiological time series and less information processing. Multiscale Entropy (MSE) is an effective algorithm used to measure the complexity of a time series by calculating sample entropy across multiple time scales (Costa et al., 2002). De-trended fluctuation analysis (DFA) is a computational method that allows the quantification of fractal-like patterns within fluctuating time series and characterizes its dynamics (Peng et al., 1995). These methods overall measure the complexity of physiological time series which refers to the dynamical richness of a physiological signal and reflects the level of adaptability of the physiological system (Goldberger et al., 1990). When physiological systems become less complex, their information content is reduced, making them less adaptable and more rigid in response to intrinsic and extrinsic challenges (Frey et al., 2011; Goldberger et al., 1990).

Recent evidence has suggested that the pattern analysis of SpO2 has the potential to identify the negative consequences of hypoxia in healthy subjects (Costello et al., 2020). Based on recent studies, graded normobaric hypoxia leads to a corresponding increase in SpO2 entropy. Increased SpO2 entropy is indicative of enhanced engagement and adaptability of respiratory control during hypoxia in healthy individuals (Costello et al., 2020). COPD is a progressive disease leading to chronic hypoxemia and altered respiratory dynamics (Al Rajeh et al., 2021). While hypoxia is known to increase the entropy and complexity of SpO2 signals in healthy individuals, its effect on patients with chronic respiratory disease is not well understood. Clinical reports have indicated that patients with COPD have altered sensitivity to oxygen and carbon dioxide, which may indicate impaired central respiratory control system during the course of the disease following chronic hypoxia (Lane and Howell 1970). However, the integrity of the respiratory control system in patients with COPD has not been estimated non-invasively in comparison with healthy individuals. Al Raje et al. (Al Rajeh et al., 2021), have recently reported that alterations in SpO2 entropy and the fractal-like exponent have the potential to detect exacerbations in COPD. However, in this study, the SpO2 pattern is not compared with an age-matched healthy group. Therefore, in this study, we recorded SpO2 time series from patients with COPD on two occasions (24 hrs after hospitalization and at the time of discharge) and compared the non-linear pattern of SpO2 signals in a group of age and gender-matched comprised healthy individuals.

Material and Methods

Participants characteristics

The study was registered and approved by the Ethics Committee of Arak University of Medical Sciences under the reference number IR.ARAKMU.REC.1400.160. All participants in both groups were fully informed about the aims of the research project and gave their voluntary consent before participation.

We enrolled 22 patients with COPD who were hospitalized in the Pulmonology ward of Amiralmomenin Hospital (Arak, Iran). The patients were included if they had a confirmed diagnosis of COPD according to guidelines established by the Global Initiative for COPD (Ritchie et al., 2021). Patients were excluded if they had an existing diagnosis of congestive heart failure. 6 patients were discharged without notice to the re-

TABLE 1: shows a summary of the baseline demographics of patients with COPD. All data are expressed as mean ±SD

	Age	BMI	6MWT	FEV1	mMRC dyspnea scale
COPD patients	67.85±9.79	21.1±2.67	135.5±118	39.13±15.31	2.18±1.25

mMRC Dyspnea Scale: Modified Medical Research Council *Dyspnea Scale*

TABLE 2: Summary of the mean and variability indices of SpO2 in patients with COPD during the hospitalization and discharge phases and in control subjects. All data are expressed as mean ±SD. * Compared to Control.

Groups / Parameters	Control	COPD Hospitalization	COPD Discharge
Age	61.15± 8.49	67.85±9.79	67.85±9.79
BMI	23.24±3.984	21.1±2.67	21.1±2.67
Mean SpO2	96.21± 0.78	90.27± 1.37****	90.73 ± 1.34 ****
CV	0.0061± 0.0024	0.0083± 0.003	0.0073± .0029
SD	0.575± 0.225	0.7408± 0.364	0.663± 0.267
Sample Entropy	1.015 ± 0.138	0.783 ± 0.193 ***	0.778 ± 0.285 **
DFA (α1)	1.32 ± 0.08	1.412 ± 0.128 *	1. 417 ± 0.085 **
DFA (α2)	0.821 ± 0.092	0.958± 0.138 **	0.939 ± 0.197 *

search staff. Additionally, the recording quality of SpO2 was found to be poor in three patients. Consequently, these participants were excluded from the analysis. The study included a total of 13 participants diagnosed with COPD, with an average age (SD) of 67.85 (9.79) years. The baseline clinical characteristics of the COPD patients are provided in Table 1. For the control group, we enrolled 16 age- and sex-matched participants in good health, with an average age (SD) of 61.15 (8.49) years (Table 2). In the control group, participants with a history of smoking, pulmonary and cardiovascular diseases, sickle cell anemia, or recent use of medications affecting the respiratory or autonomic nervous systems within the past month were excluded. In the control group, none of the recruited participants chose to withdraw from the research. Therefore, the data from all participants in this group were considered for analysis.

Data Collection

Data collection was conducted from August 27 to November 20, 2019. SpO2 levels were recorded using pulse oximetry from the index finger of one hand in all subjects. The signals from the pulse oximeter were digitized at a sampling rate of 1 kHz, and the recorded data was automatically downsampled by a factor of 1000 to 1 sample per second (1/s) by the recording device. Pulse oximeter recordings for COPD patients were conducted at two different time points: 24 hrs after admission to the hospital (during hospitalization) and right before discharge. In this research, 25 mins of continuous SpO2 time series were used for the computation of SpO2 variability indices.

Linear pattern analysis of oxygen saturation (SpO2) variability

Traditional linear SpO2 variability analysis, including mean SpO2 and standard deviation, is used to identify the general behavioral characteristics of the time series.

Non-linear pattern analysis of oxygen saturation (SpO2) variability

Nonlinear Pattern analysis of SpO2 focuses on the complexity of SpO2 dynamics. In this research, three non-linear methods based on information and fractal theories were conducted: Sample Entropy, MSE, and DFA. These techniques can provide valuable insights

into the underlying physiological processes.

Sample Entropy

Sample entropy can be used to investigate the temporal dynamics of physiological signals. This index quantifies the degree of regularity versus unpredictability in the time series (Richman and Moorman 2000). Sample entropy is defined as the negative natural logarithm of the conditional probability that two sequences, which are similar for m points, remain similar at the next point within a tolerance (r) while excluding self-matches. In our analysis, we set the values for these parameters as m=2 and r=0.2 (Bhogal and Mani 2017). Higher sample entropy values indicate a more irregular and unpredictable time series, while lower sample entropy values reflect a more regular and predictable time series.

Multiscale Entropy

Multiscale entropy analysis (MSE) can be utilized to quantify the complexity of physiological time series across multiple scales. Traditional entropy-based algorithms can only quantify the single entropy of a physiological time series, while MSE uses a coarse-graining procedure that creates new time series by averaging the time points. The entropies of the new time series are estimated and plotted against the scales (Costa et al., 2005). The sequential changes over different time scales give information about the complexity of physiological signals

Detrended fluctuation analysis

Detrended fluctuation analysis (DFA) provides a mathematical technique for quantifying the autocorrelation properties that are embedded in apparently non-stationary physiological data (Peng et al., 1995). In this technique, the root mean square of the fluctuation is measured in the integrated and detrended time series data. The measurement is performed within time windows of various sizes, which are then plotted against window size on a log-log scale. The slope of the plot, defined by the α exponent or autocorrelation exponent, represents the fractal correlation property of the time series. An α exponent $\alpha = 0.5$ corresponds to random white noise and an uncorrelated process. When $0.5 \leq \alpha \leq 1$, it indicates long-range power-law correlations. Lastly, an α value of 1 indicates long-range power-law correlations of the 1/f fractal-like dynamics. For $\alpha > 1$, correlations exist but are no longer in the power-law form, whereas $\alpha = 1.5$ corresponds to Brownian motion or a random walk.

Statistical analysis

Statistical analysis was performed using PRISM 8 (GraphPad, La Jolla, CA, USA) with significance set at $p < 0.05$. The normality of the data was checked using the Shapiro–Wilk test. Data are shown as mean ± SD unless otherwise specified. Comparisons between healthy subjects and patients were made using the unpaired t-test and the Mann-Whitney U test. Additionally, comparisons of data between the hospitalization and discharge time of patients with COPD were conducted using the paired t-test and Wilcoxon test. Two-way ANOVA analysis was employed to determine the effect of both healthy status and COPD disease on the MSE values. Lastly, Spearman's correlation coefficients were employed to evaluate the correlation between SpO2 sample entropy and SpO2 mean.

Results

Overall SpO2 signals from thirteen patients were used in this study. The mean (SD) duration of hospitalization was 5 (1) days. All patients survived hospitalization and were discharged following a course of therapy.

An example of SpO2 signals is shown for healthy participants and patients with COPD in Figure 1. The SpO2 signals display a complex pattern of fluctuation in both control and COPD participants. The SpO2 variability indices are presented in Table 2. Overall, the mean SpO2 during hospitalization was not statistically different from that at discharge (90.27± 1.37% vs. 90.73 ± 1.34 %; $p = 0.335$). However, the mean SpO2 in control subjects was 96.2 ± 0.78, which is within the normal range and significantly higher than the levels observed during hospitalization and at discharge time ($p < 0.0001$). Additionally, the coefficient of variation (CVs) for both recording times of COPD subjects were similar, which was non-significantly higher than the control group ($p = 0.0809$) (Table 2). Similarly, the mean standard deviation (SD) of SpO2 variations of the groups were also similar (Table 2).

No statistically significant differences were observed between the hospitalization and discharge time in SpO2 complexity parameters, including DFAα1, DFAα2, sample entropy, and MSE. The mean SpO2 sample entropy

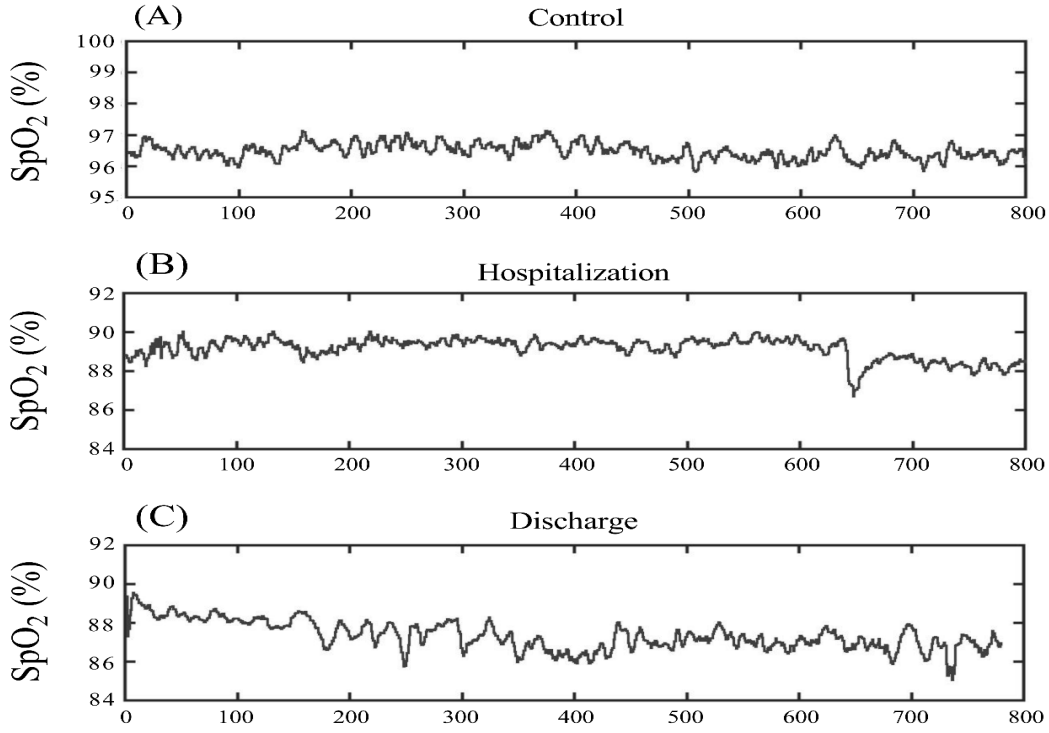

FIGURE 1. Representative SpO2 signals recorded from control subjects (A) and with COPD during the hospitalization phase (B) and discharge phase (C). The X-axis is the data points of the recorded pulse oximeter signals and the Y-axis is the SpO2 (%).

was higher in healthy individuals in comparison with patients with COPD during hospitalization (1.015 ± 0.152 vs 0.783 ± 0.193; p=0.0001) and discharge time (1.015 ± 0.152 vs 0.778 ± 0.285; p=0.0018).

The relationship between SpO2 sample entropy and the mean SpO2 was also examined (Figure 2), and the graph showed that there was no linear relationship between the two variables (r = 0.0014, p=0.997), (r = 0.1923, p=0.529), and (r = 0.449, p=0.124), in control, COPD hospitalization, and discharge respectively groups

MSE analysis demonstrated qualitative similarity in the profiles of MSE between both control subjects and those with COPD. Moreover, an increasing trend of sample entropy values was observed in both control and COPD participants at all scales (Figure 3), indicating the complex nature of fluctuated SpO2 time series (Al Rajeh et al., 2021; Costa et al., 2002). Patients with COPD, however, had a significantly reduced sample entropy at different scales according to two-way ANOVA. This emphasizes the decreased complexity and information content of the physiological system in pathological conditions (Goldberger et al., 1990).

Through DFA analysis, the short-term scaling exponent (α1) and long-term scaling exponent (α2) of SpO2 data were examined. The α1 values observed in the control subjects were (1.32 ± 0.08), ranging between those of pink noise (1/f dynamics) and Brownian motion. In contrast, there was a significant increase in the α1 values of COPD patients during their hospitalization (1.412 ± 0.128) and at discharge (1.417 ± 0.085). These values display a considerable degree of similarity analogous to that observed in Brownian motion. (α = 1.50). Furthermore, the α2 values observed in both the control and COPD groups fall within the range between those of white noise and pink noise. However, the α2 values in both recording conditions of COPD patients showed a significant difference when compared to the control group (table 2).

Discussion

This study tested the hypothesis of whether the entropy and fractal-like behavior of SpO2 signals are altered in patients with COPD. The sample entropy and multiscale entropy (MSE) across different scales decreased, while both the short-term scaling exponent (α1) and the long-term scaling exponent (α2) exhibited alterations in patients with COPD in comparison with healthy con-

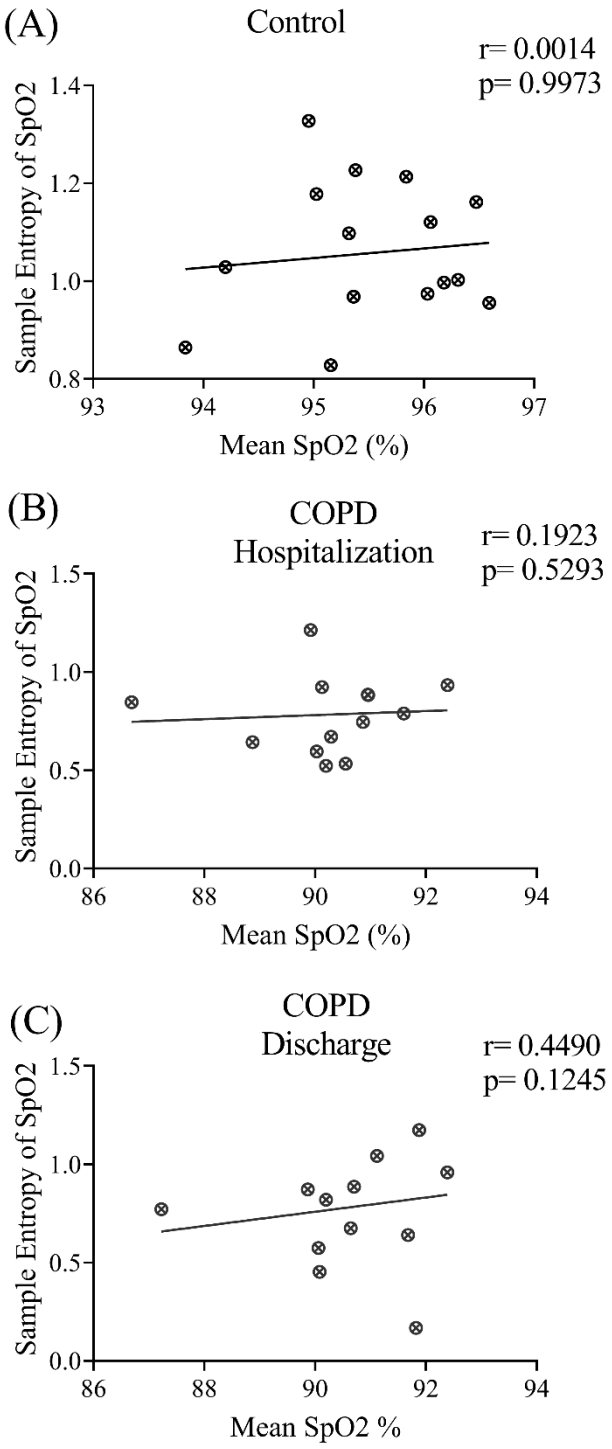

FIGURE 2. Graph showing the correlation between mean SpO2 level and sample entropy of SpO2. Each point represents a participant in the study. r and p represent the Spearman correlation coefficient and p-value, respectively.

trols. Our findings suggest that patients with COPD exhibited a significant reduction in SpO2 complexity in comparison to the healthy subjects.

SpO2 complexity, derived from non-linear analysis, focuses on measuring the underlying complexity of non-stationary biological signals (Bhogal and Mani 2017). A healthy subject can adapt to a dynamic environment through the complex interactions of multisystem components. In diseased conditions, the balance between stability and adaptability becomes impaired in response to intrinsic or extrinsic stimuli, resulting in a decrease in complexity (Frey et al., 2011; Goldberger et

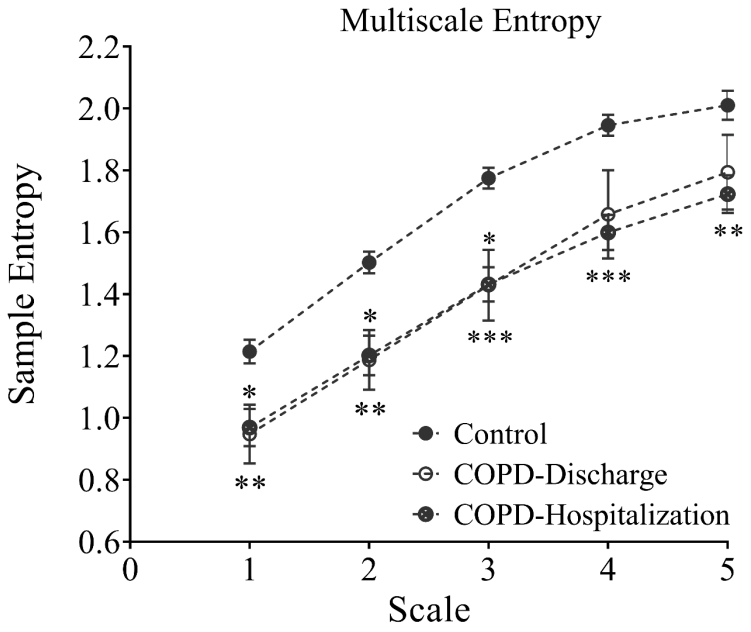

FIGURE 3. The Multiscale Entropy (MSE) graph illustrates the overall complexity of the patients with COPD during the hospitalization and discharge phases and the control subjects. The error bars are ± standard error of the mean values.

al., 1990). Pattern analysis of SpO2 variability has the ability to quantify this complexity, and it has been studied in a number of diseases with promising results. It has been associated with improvements in the diagnosis of sleep apnea-hypopnea syndrome (Vaquerizo-Villar et al., 2018), prognosis of survivability in patients with sepsis (Gheorghita et al., 2022), and prediction of exacerbation in individuals with COPD (Al Rajeh et al., 2021).

Based on theoretical studies, Pincus (1994) proposed that the entropy of physiological time series decreases with disease and pathology, indicating an increased system isolation (Pincus 1994). Experimental studies have also provided evidence of a significant change in the entropy of heart rate variability during diseases (Gholami et al., 2012; Tsai et al., 2019; Tsai et al., 2020). Similarly, similar results have been observed in the analysis of SpO2 variability in non-survival sepsis patients (Gheorghita et al., 2022). Reduced entropy can be interpreted as a decline in the connectivity of the physiological network (Pincus 1994). We have also observed a similar change in SpO2 variability in patients with COPD during utilizing sample entropy and MSE analysis. The lower sample entropy values observed at each scale during hospitalization, and also at different scales during discharge, suggest a decrease in complexity and a possible increase in partial isolation of the respiratory control system during the course of COPD.

The entropy of a physiological time series quantifies the information content transfer between components within a control system (Pincus 1994). It is logical to suggest that fluctuations in SpO2 may provide meaningful information regarding the respiratory system's integrity. Previous studies have shown that investigating the SpO2 pattern allows quantification of the engagement of the respiratory control system in response to environmental challenges. Previous reports have shown an inverse correlation between mean SpO2 and SpO2 Sample Entropy in healthy individuals during exposure to normobaric hypoxia, indicating that lower oxygen saturation is associated with higher SpO2 entropy (Costello et al., 2020; Jiang et al., 2021). This increase in sample entropy in response to hypoxia challenges suggests greater amounts of information being processed within the respiratory control system network (Costello et al., 2020; Jiang et al., 2021). Increased entropy of SpO2 signals can be interpreted as a higher degree of engagement of the components within a respiratory control system (Jiang et al., 2021). Interestingly, based on our findings, the mean SpO2 in patients with COPD is significantly lower than control in both the discharge and hospitalized phases of the study, indicating the presence of chronic

hypoxia in this patient population. In addition, the patients' SpO2 sample entropy was lower than the control group, and there was no correlation observed between the mean SpO2 and SpO2 sample. This finding suggests a notable impairment in the cardiorespiratory integrity of patients with COPD, consistent with the reduced complexity of OSV signals observed in patients with COVID-19 (Alassafi et al., 2024) and COPD (Al Rajeh et al., 2021). The mechanism behind this phenomenon might reflect the compensatory mechanism involved during adaption to chronic hypoxemia in COPD and alterations in sensitivity to oxygen and CO2 which is consistently reported in patients with COPD. However, the advantage of our analysis is that it can provide a non-invasive method to estimate the integrity of respiratory control using short-term analysis of a pulse oximeter which is available in more healthcare settings.

The purpose of applying DFA to oxygen saturation (SpO2) fluctuations analysis is to determine the fractal-like behavior of physiological time series (Peng et al., 1995). DFA of SpO2 signals results in two scaling exponents, α1 and α2 due to a crossover in the DFA graphs (Bhogal and Mani 2017). In SpO2 variability analysis, the α1 of healthy adult subjects is reported to be ~ 1.30, and α2 is around 0.87 (Bhogal and Mani 2017). Our study reveals a comparable crossover effect where α1 falls between pink noise and Brownian motion (1.34), while α2 lies between white noise and pink noise (0.82). The fluctuation of SpO2 appears to be highly stable on very short scales, leading to a higher α1 value. However, on larger scales, there is greater fluctuation, indicating a more complex behavior (Bhogal and Mani 2017). Based on prior studies, when α is equal to 1.5 indicates Brown motion and the presence of positive autocorrelation and smooth fluctuations (Peng et al., 1995). High autocorrelation indicates a strong relationship between current and past values, making prediction easier (Lefebvre et al., 1993; Sugihara and May 1990). Table 2 demonstrates a significantly higher α1 and α2 during in patients with COPD in comparison with healthy controls. Autocorrelation can provide information about the stability and memory of a complex system (Satti et al., 2019). In severe asthma, the high value of the α exponent that is computed from PEF data suggests longer memory in the respiratory system (Shirazi et al., 2013; Thamrin et al., 2011). The longer memory of systems causes the environmental challenges to be less able to alter the dynamics of the system and thus may reduce the system's adaptability to external challenges (Frey et al., 2011). Therefore, according to our results, lower entropy and higher autocorrelation of the SpO2 signal may suggest partial system isolation and less controllability of the respiratory system, with a decreased response to environmental stimuli in patients with COPD.

This study has several limitations. First, the small sample size prevents establishing a relationship between the severity of COPD disease and the magnitude of change in the complexity parameters. However, despite the small sample size, the results generally showed a significant reduction in the complexity of the SpO2 signal in COPD. Second, given the unstable condition of patients upon admission, it was not possible to record the SpO2 signal during the first 24 hrs of hospitalization. Therefore, recording the patient's SpO2 on admission and before therapeutic intervention may provide more insightful information on the adaptation of the respiratory control system during the exacerbation phase of COPD. Third, due to the need to prevent patients from receiving supplemental oxygen during SpO2 data recording, the absence of supplemental oxygen administration for periods longer than 30 minutes results in intolerable hypoxia in some of the patients. Therefore, the duration of data recording for all patients was limited to approximately 25 minutes. We used 25-minute signals for pattern analysis of SpO2. As shown in previous studies, the calculation of SpO2 entropy from 30 30-minute time series provides insight into the functional state of cardiorespiratory control under hypoxic conditions (Jiang et al., 2021).

In conclusion, this study suggests altered oxygen saturation dynamics and reduced adaptability of the respiratory control system in patients with COPD. The decrease in entropy and increase in the autocorrelation exponent of the SpO2 signals suggest a decline in complexity within the SpO2 signals of COPD patients. Future studies can expand this report and investigate the role of SpO2 entropy or DFA analysis in monitoring patients with chronic respiratory diseases such as COPD.

Conclusion

The present study has established the pattern analysis of capillary SpO2 variability in hospitalized patients with COPD. The application of complexity analysis methods provided new information about the complex-

ity and regularity of this variability. The respiratory control system in patients with COPD shows less complexity and Adaptability. These non-invasive analysis methods hold promise for potential clinical applications to monitor the integrity of respiratory control in individuals with chronic respiratory disease.

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