

# Exercise-Induced Oxygen Desaturation Increases Arterial Stiffness in Patients with COPD During the 6MWT

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**Objective:** Given the established impact of exercise in reducing arterial stiffness and the potential for intermittent hypoxia to induce its elevation, this study aims to understand how oxygen desaturation during exercise affects arterial stiffness in individuals with COPD.

**Methods:** We enrolled patients with stable COPD from China-Japan Friendship Hospital from November 2022 to June 2023. The 6-minute walk test (6-MWT) was performed with continuous blood oxygen saturation (SpO<sub>2</sub>) monitoring in these patients. The patients were classified into three groups: non-exercise induced desaturation (EID), mild-EID and severe-EID, according to the changes in SpO<sub>2</sub> during the 6-MWT. The Cardio-Ankle Vascular Index (CAVI) and the change in CAVI ( $\Delta$ CAVI, calculated as CAVI before 6MWT minus CAVI after the 6MWT) were measured before and immediately after the 6MWT to assess the acute effects of exercise on arterial stiffness. GOLD Stage, pulmonary function, and other functional outcomes were also measured in this study.

**Results:** A total of 37 patients with stable COPD underwent evaluation for changes in CAVI ( $\Delta$ CAVI) before and after the 6-MWT. Stratification based on revealed three subgroups: non-EID (n=12), mild-EID (n=15), and severe-EID (n=10). The  $\Delta$ CAVI values was  $-0.53$  ( $-0.95$  to  $-0.31$ ) in non-EID group,  $-0.20$  ( $-1.45$  to  $0.50$ ) in mild-EID group,  $0.6$  ( $0.08$  to  $0.73$ ) in severe-EID group. Parametric tests indicated significant differences in  $\Delta$ CAVI among EID groups ( $p = 0.005$ ). Pairwise comparisons demonstrated significant distinctions between mild-EID and severe-EID groups, as well as between non-EID and severe-EID groups ( $p = 0.048$  and  $p = 0.003$ , respectively). Multivariable analysis, adjusting for age, sex, GOLD stage, diffusion capacity, and blood pressure, identified severe-EID as an independent factor associated with  $\Delta$ CAVI ( $B = 1.118$ ,  $p = 0.038$ ).

**Conclusion:** Patients with COPD and severe-EID may experience worsening arterial stiffness even during short periods of exercise.

**Keywords:** COPD, arterial stiffness, exercise-induced oxygen desaturation, rehabilitation

## Introduction

Exercise-induced oxygen desaturation (EID) is prevalent among chronic obstructive pulmonary disease (COPD) patients, affecting 52.6%–62.1% of individuals during the 6-minute walk test (6-MWT) when defined by a minimum blood oxygen saturation (SpO<sub>2min</sub>) below 90% or a decline of  $\geq 4\%$ .<sup>1</sup> Patients with COPD and EID may experience challenges with high-intensity exercise, necessitating healthcare professionals to adjust training intensity and/or recommend periods of rest to minimize the occurrence of oxygen desaturation,<sup>2</sup> potentially impacting training effectiveness.<sup>3</sup> Furthermore, EID may have adverse implications for the cardiovascular system, particularly concerning arterial stiffness.

In COPD patients, reduced blood oxygen saturation during the 6-MWT has been associated with an elevated mortality rate,<sup>4</sup> revealing various potential physiological and pathological mechanisms. Notably, systemic hypoxia may exacerbate the rise in arterial stiffness, contributing to an increased incidence of cardiovascular events.<sup>5</sup> Moreover, a population-based cohort study reported that severe COPD (GOLD 3–4), age  $\geq 60$ , and cardiovascular disease (CVD) are linked to increased arterial stiffness, after adjusting for confounders, only severe COPD, not productive cough, remains significantly associated with increased arterial stiffness.<sup>6</sup> Meanwhile, another study investigated the association between COPD and arterial stiffness using carotid femoral pulse wave velocity (cf-PWV). Results showed that COPD patients had greater arterial stiffness than healthy controls, particularly those with severe COPD.<sup>7</sup>

The heightened arterial stiffness is closely linked to atherosclerosis development, a condition strongly correlated with cardiovascular events such as heart disease and stroke.<sup>8</sup> Arterial stiffening can aggravate vascular blockages and narrowing, thereby elevating the risk of cardiovascular events. Additionally, increased arterial stiffness is associated with hypertension,<sup>9</sup> a contributing factor to cardiovascular risk in COPD patient.<sup>10</sup> Recognizing the established impact of exercise in mitigating arterial stiffness and intermittent hypoxia in inducing its elevation, this study seeks to precisely delineate the mechanisms through which hypoxic episodes during physical activity contribute to alterations in arterial stiffness in individuals with COPD. Furthermore, our literature search identified a lack of reports examining how EID specifically affects arterial stiffness in patients with COPD.

While EID may induce early changes in arterial stiffness among COPD patients, its comprehensive effects on the cardiovascular system remain inadequately assessed. Importantly, many COPD patients experiencing EID lack overt symptoms, and their resting SpO<sub>2</sub> levels remain within the normal range ( $\geq 92\%$ ), leading to a non-routine recommendation of oxygen supplementation during exercise.<sup>11</sup> To delve deeper into the repercussions of exercise on arterial stiffness in COPD patients, we conducted a controlled cross-sectional study investigating the acute effects of exercise on arterial stiffness in this population. This study aims to understand how oxygen desaturation during exercise affects arterial stiffness in COPD patients.

## Method

### Patients

The study protocol was reviewed and approved by the China-Japan Friendship Hospital (2022-KY-024; trial registration number: NCT04318912). Patient data confidentiality was strictly maintained, and all procedures were in compliance with the Declaration of Helsinki.

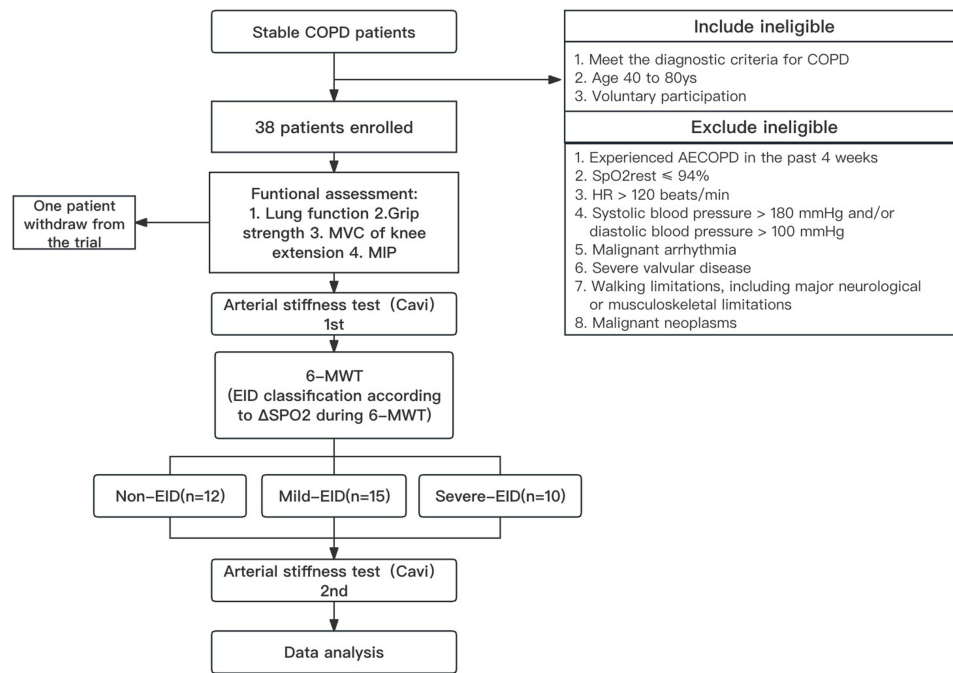
From November 2022 to June 2023, patients with stable COPD who were regularly followed up at the China-Japan Friendship Hospital were included in the study, and all patients provided informed consent. The inclusion criterion was a diagnosis of stable COPD according to the 2020 update of the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD). The exclusion criteria were as follows: (1) SpO<sub>2rest</sub>  $\leq 94\%$  (2) heart rate (HR)  $> 120$  beats/min; (3) systolic blood pressure  $> 180$  mmHg and/or diastolic blood pressure  $> 100$  mmHg; (4) malignant arrhythmia; (5) severe valvular disease; (6) walking limitations, including major neurological or musculoskeletal limitations; and (7) malignant neoplasms. The included patients completed functional assessments including lung function, grip strength, MIP, MVC, and measurements of a 6-minute walking experiment. The specific experimental flowchart is shown in [Figure 1](#).

### EID Definition and Classification

The presence or absence of EID and the severity of EID were defined based on changes in SpO<sub>2</sub> during a 6MWT test. Non-EID was defined as SpO<sub>2rest</sub> minus SpO<sub>2min</sub>  $< 4\%$  and SpO<sub>2min</sub>  $\geq 90\%$ . Mild-EID was defined as SpO<sub>2rest</sub> minus SpO<sub>2min</sub>  $\geq 4\%$  but SpO<sub>2min</sub>  $\geq 90\%$ . Severe-EID was defined as SpO<sub>2rest</sub> minus SpO<sub>2min</sub>  $\geq 4\%$  and SpO<sub>2min</sub>  $< 90\%$ .<sup>4</sup>

### 6 Minutes Walking Test (6MWT)

The 6MWT is performed as a 30-m straight walk indoors in the presence of at least two experienced assessors in accordance with American Thoracic Society (ATS) guidelines.<sup>12</sup> SpO<sub>2</sub> was continuously measured using a finger pulse



**Figure 1** Flowchart of this study.

**Abbreviations:** MIP, maximum inspiratory pressure; MVC, maximum voluntary contraction; EID, exercise induced desaturation; Cavi, Cardio-ankle vascular index; 6-MWT, 6 minutes walking test; HR, Heart rate.

oximeter, which transmits data in real time via Bluetooth and data are collected every 3 s to determine SpO<sub>2</sub>rest and SpO<sub>2</sub>min from 1 min before the start of the 6MWT to 4 min after the end of the 6MWT.

## Grip Strength

Grip strength on the dominant side was assessed using the Grip Strength Tester (KDG Grip Strength Tester). Patients were seated and instructed to let both arms hang at their sides, with the elbows extended. They were then asked to grip as forcefully as possible, ensuring that the elbow joints remained straight throughout the test.

## Maximal Voluntary Contraction (MVC) of Knee Extension

For the maximal voluntary contraction (MVC) of knee extension, a hand-held dynamometer (MicroFET 2; Hoggan, West Jordan, UT) was utilized. During the knee extension MVC test, Patients sat on a specially designed high chair with thigh straps for stabilization. The lower legs were suspended outside the chair, maintaining a knee flexion of 90° for testing on both sides. A minimum of three attempts of each side measure was made, within 10% error, and The data obtained by averaging the best values from measurements on both sides will be subjected to analysis.

## Maximum Inspiratory Pressure (MIP)

Voluntary MIP was measured at residual capacity (RV) using a portable inspiratory muscle training system (KH2; Power breathe; UK) according to ERS` statement.<sup>13</sup>

## Arterial Stiffness

The cardio-ankle vascular index (CAVI) was measured using the CAVI-Vasera VS-1000 vascular evaluation system (Fukuda Denshi, Beijing, China) before and immediately after the 6MWT to reflect the acute effect of exercise on arterial stiffness. To standardise the CAVI after de 6MWT, the tests were conducted between 9:00 AM and 11:00 AM, participants were instructed not to engage in strenuous activities, drink coffee or strong tea, overeat, or remain in a state of hunger on the day before and the day of the test. During the measurement, participants were supine;

electrocardiogram electrodes were placed on both wrists, a microphone for monitoring heart sounds (phonocardiogram) was placed on the sternum to collect first and second heart sounds, and four standard blood pressure cuffs were wrapped around the upper arms and ankles as directed. The CAVI value was automatically calculated by the software as mentioned before.<sup>14</sup> Details of the formula and repeatability of the index have been published earlier.<sup>14</sup> In this study, the average CAVI of the values obtained for the left and right sides was calculated for later analysis. The system measured both HR and blood pressure.

## Lung Function

Lung function assessment was performed by trained hospital staff by using the Jaeger<sup>®</sup> Masterscreen system (Jaeger<sup>®</sup>, Viasys Healthcare GmbH, Hochberg, Germany) according to the ATS and European Respiratory Society (ERS) guidelines.<sup>15</sup> The following respiratory parameters were documented: the ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC), forced vital capacity (FVC), FVC as a percentage of the predicted value(FVC%), forced expiratory volume in one second (FEV1), FEV1 as a percentage of the predicted value(FEV1%), and diffusion capacity (DLCO-SB). Additionally, the DLCO-SB as a percentage of the predicted value(DLCO-SB%) was recorded.

## Sample Size

Based on the pilot study data, the mean change in CAVI for the Non-EID group is  $-0.7$ , for the mild-EID group is  $-0.4$ , and for the severe EID group is  $+0.4$ . The standard deviation of the change in CAVI across the three groups is  $0.65$ . With a two-sided alpha of  $0.05$  and a power of  $0.9$ , calculations using PASS software version 14.0.9 suggest a sample size of 10 subjects per group, totaling 30 subjects at least.<sup>16</sup>

## Statistical Analysis

Statistical analysis was performed using SPSS 25.0 (SPSS Inc., Chicago, Illinois). The Shapiro–Wilk test was used to analyze the normality of the data. Continuous variables are described as mean  $\pm$  SD values. Continuous variables were normally distributed, and analysis of variance (ANOVA) was used among multiple groups of independent samples. If the distribution was skewed, the Kruskal–Wallis test was used for comparison among multiple groups of independent samples, and the results were described as mean and standard deviation or median and interquartile range (IQR) according to the data distribution. For pairwise mean comparisons among three groups, if the data follow a normal distribution and have equal variances, use independent samples *t*-tests with multiple comparison corrections (eg, Bonferroni correction). If the data do not follow a normal distribution, use the non-parametric Mann–Whitney *U*-test with multiple comparison corrections.

To compare the CAVI values of the same patient before and after the 6WMT, and to display the results for three groups, a paired *t*-test was used. Spearman correlation analysis was used to investigate the correlation between EID degree and demographic characteristics, lung function, functional evaluation index and so on. Multiple linear regression analysis was used to analyze the factors affecting the change of CAVI, and to analyze whether EID was an independent influencing factor of CAVI when adjusting the influencing factors of age, gender, GOLD stage, diffusion function and blood pressure on the change of arterial stiffness, and dummy variables were set for the influencing factors. A *p*-value of  $<0.05$  was considered statistically significant.

## Results

### Participant Characteristics

Overall, 38 patients with COPD without resting oxygen desaturation were recruited through outpatient screening and evaluation of inpatient medical records. Among them, three were excluded because their forced expiratory volume at 1 s/forced vital capacity (FEV1/FVC) was  $>70\%$  after the pulmonary function test review before entering the study. One patient was dropped from the study early owing to dizziness during an exercise test (later diagnosed as left subclavian steal syndrome) and not included in the analysis. In this study, all participants who successfully completed the trial

underwent an EID evaluation and its severity, determined by assessing changes  $\text{SpO}_2$  during the 6MWT ( $\Delta\text{SpO}_2 = \text{SpO}_{2\text{rest}} - \text{SpO}_{2\text{min}}$ ). In the cohort, 12 individuals exhibited no evidence of EID, while 15 participants had mild-EID. Notably, 10 patients had severe-EID, characterized by a substantial decline in  $\text{SpO}_2$  during exercise. Anthropometric characteristics, arterial stiffness at baseline and after 6MWT, exercise capacity (including the 6-minute walking distance, grip strength, maximum inspiratory pressure, and knee extension muscle strength), and vital signs were not significantly different among the three EID groups (Table 1). However, FEV1/FVC and diffusion capacity (predicted diffusing capacity for carbon monoxide [DLCO] %) in patients with severe-EID were lower than those in patients with non-EID and mild-EID ( $p < 0.05$ ).

## Changes in Arterial Stiffness in Patients with COPD and Different Degrees of EID

The  $\Delta\text{SpO}_2$  of the three groups was as follows: non-EID group, 1.5 (–2 to –1); mild-EID group, –5 (–6 to –4); and severe-EID group: –11 (–14 to –9). Non-parametric test results showed significant differences in the  $\Delta\text{SpO}_2$  between patients with varying degrees of EID ( $p < 0.01$ ). Pairwise comparison also showed significant differences among different degrees of EID patients. (Figure 2A). The changes in CAVI before and after exercise were different in patients with different degrees of EID. CAVI in non-EID patients decreased significantly after exercise (CAVI be:  $8.96 \pm 2.21$ , CAVI af:  $8.29 \pm 1.94$ ;  $p = 0.004$ ), CAVI significantly increased in patients with severe-EID (CAVI be:  $8.02 \pm 1.47$ , CAVI af:  $8.41 \pm 1.28$ ;  $p = 0.003$ ). The CAVI of patients with mild-EID before and after exercise showed a decreasing trend, but the values were not significantly different (CAVI be:  $8.87 \pm 1.26$ , CAVI af:  $8.36 \pm 1.23$ ;  $p = 0.099$ ) (Figure 2B).  $\Delta\text{CAVI}$  in the non-EID, mild-EID, and severe-EID groups was –0.53 (–0.95 to –0.31), –0.20 (–1.45 to 0.50), 0.6 (0.08 to 0.73), respectively (Figure 2B). Non-parametric test results showed significant differences in the  $\Delta\text{CAVI}$  between patients with varying degrees of EID ( $p = 0.005$ ). Pairwise comparison results showed no statistical difference between non-EID and mild-EID patients ( $p = 0.701$ ). However, there were significant differences between mild-EID vs severe-EID and non-EID vs severe-EID ( $p = 0.008$  and  $p < 0.001$ ) (Figure 2C).

## Severe-EID Was Found to Be an Independent Factor Associated with $\Delta\text{CAVI}$

EID severity was negatively correlated with FEV1 ( $r = -0.36$ ,  $p = 0.035$ ), DLCO ( $r = -0.41$ ,  $p = 0.015$ ), and predicted DLCO percentage ( $r = 0.44$ ,  $p < 0.024$ ), and positively correlated with SPB ( $r = 0.39$ ,  $p = 0.024$ ) and  $\Delta\text{CAVI}$  ( $r = 0.43$ ,  $p = 0.009$ ).

To analyze whether EID is an independent factor influencing  $\Delta\text{CAVI}$ , we performed multiple linear regression analysis, with age, sex, GOLD stage, diffusion, and blood pressure as covariates owing to their potential impact on stiffness changes. The multivariable analysis showed that severe-EID remained an independent factor for  $\Delta\text{CAVI}$  after the adjustment ( $B = 1.118$ ,  $p = 0.038$ ) (Table 2).

## Discussion

To the best of our knowledge, this is the first report on the impact of EID on arterial stiffness in patients with COPD. The primary findings of this study are as follows. First, patients with COPD and severe-EID experienced a significant increase in arterial stiffness following exercise, while non-EID patients exhibited a significant decrease in arterial stiffness after exercise, similar to the response observed in healthy individuals.<sup>17</sup> Second, the severity of EID may be an independently influences factor in the immediate post-exercise changes in arterial stiffness.

Currently, there are two predominant perspectives on the regulation of arterial stiffness. First, exercise is considered a protective factor against cardiovascular risk, because it can lead to both immediate and long-term reductions in arterial stiffness. On the other hand, hypoxia is recognized as a risk factor for the acute increase in arterial stiffness, contributing to its elevation. This study was motivated by the findings of Vanfleteren LE 's research,<sup>18</sup> which involved 129 patients with COPD undergoing a comprehensive pulmonary rehabilitation intervention centered around exercise, totaling 40 sessions. The study found that arterial stiffness in patients with COPD was not associated with systemic inflammation, nor influenced by state-of-The-art pulmonary rehabilitation interventions. This observation contrasts with the typical response of arterial stiffness to exercise seen in healthy individuals and in patients with other conditions, such as hypertension<sup>19</sup> and heart failure.<sup>20</sup> Exercise is known to immediately reduce arterial stiffness, partly through enhancing

**Table I** Baseline Characteristics of Patients with Chronic Obstructive Pulmonary Disease in Non-EID, Mild-EID, and Severe-EID Groups

Demographic Characteristics	Total	Non-EID Group	Mild-EID Group	Severe-EID Group	F	P
	n = 37(100%)	n = 12(32%)	n = 15(41%)	n = 10(27%)		
Age (years)	63.39 ± 13.91	59.92±20.07	63.53±10.92	65.86±7.90	0.42	0.66
Male	32(89%)	11	15	7		
Smoking index	289.11±502.70	334.17±549.89	426.53±504.34	264.00±504.03	0.248	0.782
Body composition						
BMI (kg m <sup>2</sup> )	24.17±2.82	23.48±2.46	24.68±2.42	25.09±3.66	1.07	0.37
Pulmonary function						
FEV1 (L)	1.92±0.73	2.25±0.69	1.80±0.69	1.58±0.76	3.41	0.05
FEV1 (% predicted)	66.85±28.15	79.17±28.70	58.55±22.61	61.74±33.43	2.65	0.09
FEV1/FVC	52.56±11.73	57.78±9.64	47.88±12.52	52.91±10.67	3.47	0.04*
FVC	3.62±0.99	3.85±0.86	3.75±0.91	2.94±1.19		0.3
FVC (% predicted)	98.11±26.47	107.61±27.85	93.72±18.46	89.87±36.05	2.97	0.07
DLCO SB	6.32±2.37	7.46±3.16	6.91±1.49	4.76±2.02	2.76	0.08
DLCO SB (% predicted)	73.79±25.60	90.60±30.47	67.36±15.64	61.83±26.73	3.93	0.03
GOLD Stage						
GOLD I	11 (30.56%)	6	3	2		
GOLD II	15 (41.67%)	5	7	3		
GOLD III	8 (22.22%)	2	4	2		
GOLD IV	3 (8.33%)	0	1	2		
Oxygen saturation						
SpO <sub>2</sub>	96.03±2.05	95.77±2.17	96.80±1.57	94.86±2.34	2.51	0.1
SpO <sub>2min</sub>	90.77±5.20	94.15±2.44	91.60±2.26	82.71±5.19	32.21	<0.01#
ΔSpO <sub>2</sub> #	-5 (-8 to -2)	-1.5(-2 to -1)	-5 (-6 to -4)	-11(-14 to -9)		<0.01#
Arterial stiffness						
CAVI be	8.69±1.70	8.96±2.21	8.87±1.26	8.02±1.47	0.71	0.5
CAVI af	8.34±1.50	8.29±1.94	8.36±1.23	8.41±1.28	0.01	0.99
ΔCAVI #	-0.20(-0.79 to 0.54)	-0.53 (-0.95 to -0.31)	0.20 (-1.45 to 0.50)	0.6 (0.08 to 0.73)		<0.01#
Hemodynamic						
Systolic pressure <sub>Before 6WMT</sub> (mmHg)	126.15 ± 14.32	120.69±12.75	126.79±14.91	136.50±11.73	2.81	0.08
Diastolic pressure <sub>Before 6WMT</sub> (mmHg)	73.52 ± 8.78	73.15±12.75	73.07±9.63	75.33±9.87	0.15	0.86

(Continued)



Table 1 (Continued).

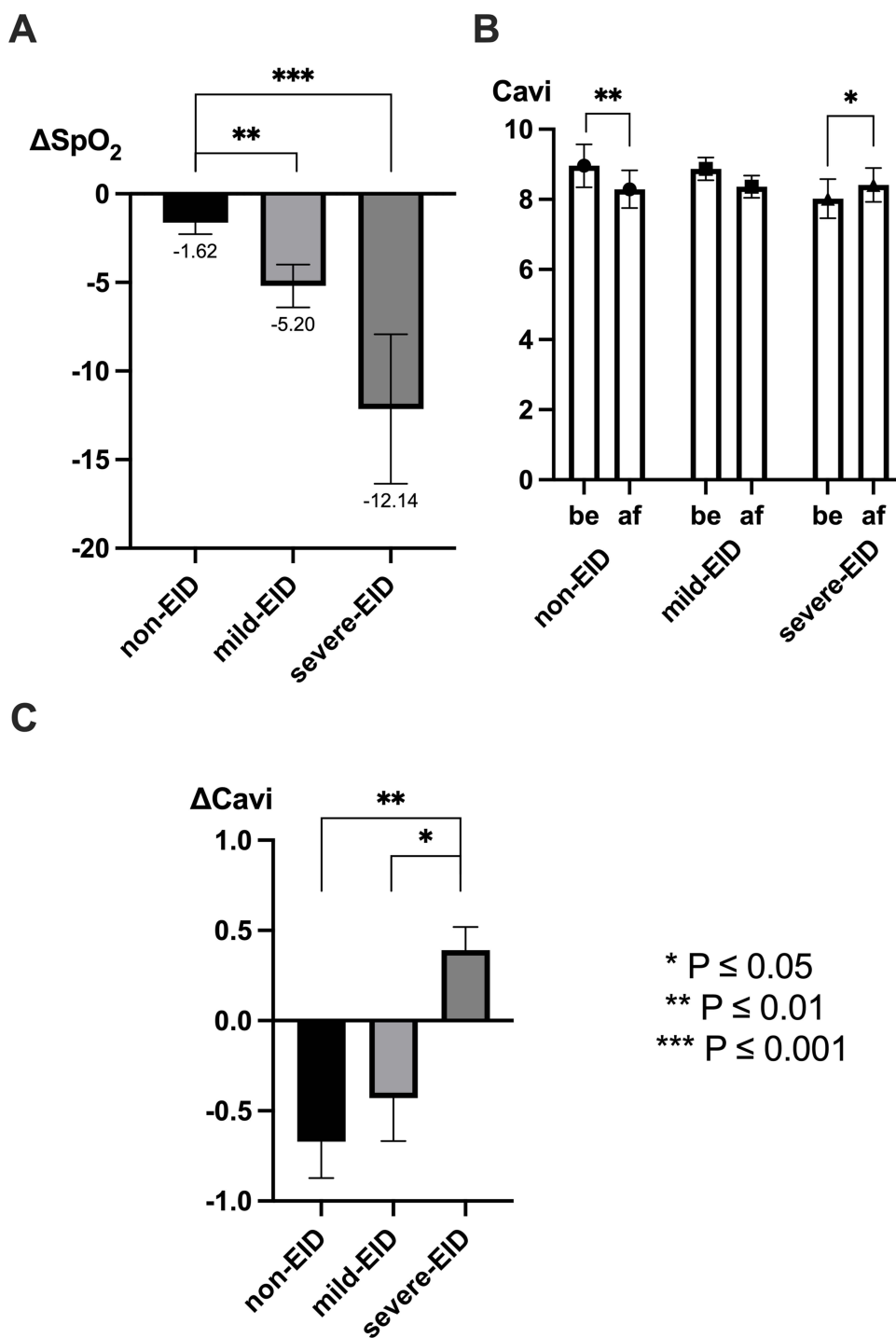
Demographic Characteristics	Total	Non-EID Group	Mild-EID Group	Severe-EID Group	F	P
	n = 37(100%)	n = 12(32%)	n = 15(41%)	n = 10(27%)		
MAP <sub>Before 6WMT</sub> (mmHg)	91.06 ±8.98	89.00±8.87	90.98±9.66	95.72±6.94	1.16	0.32
Systolic pressure <sub>after 6WMT</sub> (mmHg)	138.33±20.48	134.5±18.41	135.17±22.27	152.33±17.36	1.859	0.175
Diastolic pressure <sub>after 6WMT</sub> (mmHg)	81.27±12.92	78.67±12.45	83.91±14.72	81.17±10.82	0.478	0.625
MAP <sub>after 6WMT</sub> (mmHg)	86.00±37.58	97.25±13.09	101.08±14.11	105.00±	0.734	0.489
Dyspnea						
mMRC #	1(0 to 2)	1(0 to 1.5)	1(0.5 to 1)	3(1 to 3)		0.58
Borg at 6WMT termination #	1(0.5 to 2)	0.5(0 to 1.75)	1.0(0.5 to 1.0)	2 (1 to 7)		0.16
Fatigue						
RPE at 6WMT termination #	12(10 to 14)	10(10 to 14)	12(10 to 14)	14(10 to 16)		0.62
Functional outcomes						
6WMD (m)	473.12 ±112.77	492.92±128.97	478.67±93.41	405.00±118.76	1.14	0.33
MIP #	83.42(59.88 to 88.80)	83.04(61.67 to 93.22)	87.11(76.44 to 88.80)	52.81(50.69 to 58.43)		0.6
Grip strength #	33.95(25.35 to 37.90)	30.72(23.13 to 38.61)	35.00(32.93 to 38.06)	28.05(12.51 to 30.00)		0.11
MVC (Keen extension)	28.47±11.77	29.15±10.03	32.10±14.97	19.36±3.15	1.7	0.21

**Notes:** \*Denotes a statistically significant difference between groups, with a P value < 0.05. #These parameters presented are not normally distributed. Therefore, the median and interquartile range (IQR) are reported instead of the mean and standard deviation.

**Abbreviations:** BMI, Body mass index; FEV1, forced expiratory volume at 1 s; FVC, forced vital capacity; DLCO SB, single-breath diffusing capacity of the lung for CO; CAVI, cardio-ankle vascular index; 6WMD, 6-minute walking distance; 6WMT, 6-minute walking test; RPE, rate of perceived exertion; MIP, maximum inspiratory pressure; MVC, maximum voluntary contraction.

endothelial function,<sup>21</sup> and endothelial cells play a crucial role in regulating vascular tone and maintaining vascular flexibility. Moreover, exercise can promptly stimulate the release of nitric oxide (NO) by endothelial cells, a potent vasodilator.<sup>22</sup> Increased NO production leads to arterial wall relaxation, resulting in reduced stiffness. However, there is also evidence suggesting that another category of diseases characterized by intermittent hypoxia (IH), such as obstructive sleep apnea syndrome (OSAS), may lead to increased arterial stiffness.<sup>23</sup> IH is a hallmark feature of OSAS. The precise mechanisms linking IH to arterial stiffness are complex and multifactorial, through various pathways, including oxidative stress, inflammation, sympathetic nervous system activation, and endothelial dysfunction.<sup>24</sup>

The interplay between COPD, in addition to EID, and arterial stiffness is intricate and multifaceted. Severe-EID exacerbates the deprivation of oxygen delivery to peripheral tissues during exercise, potentially compounding exercise-induced vascular dysfunction, primarily attributed to hypoxia. Some studies have explored the relationship between systemic inflammation, oxidative stress, and their impact on the extra-pulmonary features of COPD, particularly in relation to cardiovascular risk.<sup>25,26</sup> Both systemic Inflammation and oxidative stress are recognized as significant contributors to the extra-pulmonary manifestations of COPD and are suggested to play a role in increasing cardiovascular risk in COPD patients. Also, a correlation between arterial stiffness and systemic inflammation has been found in several studies of COPD patients. C-reactive protein (CRP) can interact with endothelial cells, stimulating the production of IL-6



**Figure 2** Changes in CAVI among patients with different degrees of EID. (A)  $\Delta SpO_2$  in the non-EID, mild-EID, and severe-EID groups. (B) The changes in CAVI before and after exercise in the three groups. (C)  $\Delta CAVI$  in patients with different degrees of EID.

and endothelin-1, and altering nitric oxide (NO) production, which contributes to endothelial dysfunction. Elevated levels of IL-6 and TNF-alpha can increase the expression of adhesion molecules on activated endothelium, facilitating the formation of atherosclerotic plaques. Some studies have not found a link between inflammation and arterial stiffness in COPD. This discrepancy could be due to the assessment techniques used, the specific proteins targeted, or the limited number of inflammatory markers studied.<sup>18</sup> The relationship between arterial stiffness and novel biomarkers of systemic



**Table 2** Determination of the Independent Factors Influencing  $\Delta$ CAVI by Using Multiple Linear Regression Analysis

Variable	B 95% CI	P
Age	-0.00420 (-0.02919, 0.02079)	0.7322
Sex	-0.01737 (-1.31129, 1.27654)	0.9782
GOLD stage (with reference to stage 1)		
Stage 2	0.18758 (-0.54713, 0.92230)	0.6036
Stage 3	-0.22331 (-1.22410, 0.77748)	0.6498
Stage 4	0.36767 (-1.16702, 1.90236)	0.6260
DLCO %	0.00174 (-0.01377, 0.01724)	0.8195
SBP	-0.00438 (-0.02918, 0.02041)	0.7190
EID (with reference to non-EID)		
Mild	0.29288 (-0.41655, 1.00231)	0.4033
Severe	1.11883 (0.06727, 2.17039)	0.0380

inflammation, as well as biochemical markers of cardiac dysfunction or respiratory exacerbation, requires further investigation in COPD patients.<sup>5</sup>

EID exacerbates these perturbations by precipitating systemic hypoxia during exertion, triggering vasoconstriction, and undermining the bioavailability of NO.<sup>27</sup> On the other hand, COPD-driven chronic inflammation begets endothelial dysfunction and oxidative stress, prompting arterial remodeling and stiffening. Collectively, these dynamics disrupt the delicate equilibrium of the vascular relaxation-contraction function, culminating in heightened arterial stiffness. Furthermore, compelling research substantiates a substantial escalation in the mortality risk among patients with COPD and EID,<sup>4</sup> underscoring the pivotal role of EID in influencing the cardiovascular health trajectory of these individuals.

Our findings suggest that the relationship between arterial stiffness and exercise-induced oxygen desaturation can be partially explained by a mediating effect of accelerated aging and elastin loss. This implies that arterial stiffness may not directly cause EID but rather reflects underlying biological processes related to aging. This insight is crucial for developing targeted interventions aimed at mitigating EID, as addressing the underlying aging process or elastin degradation might be more effective than focusing solely on arterial stiffness.

By pursuing these further research directions, we aim to enhance our understanding of the complex interplay between vascular and respiratory health and improve outcomes for individuals at risk of exercise-induced oxygen desaturation. We would like to go further research, firstly, longitudinally track the progression of arterial stiffness, elastin degradation, and oxygen desaturation over time. Secondly, investigate other potential mediators and confounders to comprehensively understand the causal pathways. Thirdly, Develop and test interventions that target the identified mediators, such as treatments aimed at reducing elastin loss or slowing the aging process. By incorporating these considerations, we can enhance our understanding of the complex interplay between vascular and respiratory health and improve outcomes for individuals at risk of exercise-induced oxygen desaturation.

Our sample size calculation indicates that a minimum of 10 subjects per group is required to achieve a power of 0.9. However, we must categorize the severity of exercise-induced oxygen desaturation (EID) through the 6-minute walk test for grouping. In this study, the prevalence of severe EID is 27%. Prior to reaching the minimum sample size for this group, 12 and 15 subjects have already been included in the non-EID and mild-EID groups, respectively. This presents an objective reason for the uneven distribution of our groups, and we believe that even by continuing to expand patient recruitment, this issue cannot be resolved. Therefore, we decided to conclude recruitment once the Severe-EID group reached 10 subjects.

In conclusion, our study emphasizes the significant association between severe-EID and the immediate post-exercise increase in arterial stiffness in patients with COPD. It highlights the necessity for comprehensive cardiovascular risk management in this patient population. While our findings bear substantial implications for enhancing the cardiovascular well-being of patients with COPD, there remains a critical need for further research to comprehensively understand

arterial stiffness in this cohort, particularly regarding the impact of exercise training. The use of CAVI as a tool for evaluating immediate post-exercise changes in arterial stiffness holds substantial promise for discovering additional insights in this domain.

## Conclusion

Our data suggest that patients with COPD and severe-EID may experience worsening arterial stiffness even during short periods of exercise and that even mild-EID may counteract the exercise-induced alleviation of arterial stiffness. This finding suggests that people with COPD should avoid EID during exercise to reduce potential adverse effects on the cardiovascular system. For patients with severe-EID and COPD, oxygen support or adjustment of exercise intensity should be considered during exercise. In addition to exercise in the pulmonary rehabilitation program, light physical activity in daily life may also lead to decreased SpO<sub>2</sub> in patients with COPD. Whether it could adversely affect arterial stiffness and the determination of the optimal oxygen supplementation regimen during exercise require further research.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors have no conflicts of interest to declare in this work.

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