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Arterial Stiffness in Pre-COPD/PRISm, and COPD Stages: A Cross-Sectional Assessment of Hemodynamic Determinants

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Purpose: Arterial stiffness is associated with increased cardiovascular risk in chronic obstructive pulmonary disease (COPD). However, whether this increase reflects disease-specific vascular effects or is primarily driven by age and hemodynamic factors remains unclear, particularly in early disease states such as pre-COPD and preserved ratio impaired spirometry (PRISm). This study aimed to evaluate arterial stiffness across the COPD spectrum and to determine the independent predictors of pulse wave velocity (PWV).

Patients and Methods: This cross-sectional study included healthy controls (n=60), a combined pre-COPD/PRISm group (n=121), and COPD patients (n=120) classified according to spirometric criteria. Arterial stiffness was assessed noninvasively using brachial oscillometric PWV. Clinical characteristics, smoking exposure, spirometric parameters, symptom scores, and hemodynamic measurements were recorded. Correlation analyses and hierarchical multivariate linear regression were performed to identify independent determinants of PWV.

Results: PWV values were significantly higher in the pre-COPD/PRISm and COPD groups than in healthy controls, with the highest levels observed in COPD patients at GOLD stage E ($p<0.001$). Although PWV showed significant correlations with spirometric parameters and symptom scores in unadjusted analyses, these associations lost significance after adjustment for age and smoking exposure. In contrast, mean arterial pressure and central pulse pressure remained strongly associated with PWV ($p<0.001$). In multivariate analysis, age was the strongest independent predictor of PWV, followed by mean arterial pressure and body surface area, while FEV1% was not a significant contributor.

Conclusion: Arterial stiffness is increased not only in COPD but also in individuals with pre-COPD/PRISm. However, this increase appears to be primarily driven by age-related and hemodynamic factors rather than disease-specific airflow limitation. These findings highlight the importance of early cardiovascular risk assessment focusing on hemodynamic parameters.

Keywords: COPD, Pre-COPD, PRISm, arterial stiffness, pulse wave velocity, hemodynamic determinants

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent airflow limitation and respiratory symptoms associated with airway and/or alveolar abnormalities, often caused by significant exposure to harmful particles or gases. It is a major cause of morbidity and mortality worldwide and accounts for a large proportion of the global health burden.[1] COPD is a systemic disease that affects not only the respiratory tract but also the cardiovascular system. Increased arterial stiffness is considered an important indicator of increased cardiovascular mortality in COPD.[2,3] However, the existing literature on the effects of COPD phenotypes, particularly the predominant subtypes of emphysema and chronic bronchitis, and early-stage COPD and Pre-COPD/PRISm conditions on arterial stiffness is limited.[4,5]

Recent studies have shown that arterial stiffness is significantly increased in patients with COPD compared with healthy individuals.[3,6] This increase may be related to early pathophysiological processes such as systemic inflammation, oxidative stress, and endothelial dysfunction, which may contribute to vascular remodelling and reduced arterial

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compliance, rather than to structural lung damage specific to advanced stages of the disease.[7,8] It has been reported that these mechanisms may increase arterial stiffness by affecting vascular structure, even before the development of significant airflow limitation.[9,10]

Changes in arterial stiffness in early-stage COPD have been investigated in a limited number of studies.[11–14] Pre-COPD/PRISm and early-stage COPD (GOLD stages 1–2) represent an essential time window during which cardiovascular effects may emerge.[1] Assessments conducted at this stage may help identify cardiovascular risk earlier in COPD patients and better understand the systemic effects of the disease.[12]

The relationship between COPD and arterial stiffness in the literature is often attributed to risk factors such as smoking and aging. However, this approach fails to adequately reveal the disease-specific contributions of subclinical vascular and hemodynamic changes observed in individuals with early-stage COPD, and pre-COPD/PRISm. Recent population-based evidence has demonstrated a significant association between PRISm and increased arterial stiffness, independent of traditional cardiovascular risk factors. Notably, these studies also reported a higher prevalence of cardiometabolic comorbidities in PRISm populations. By excluding such conditions, our study provides complementary evidence suggesting that this association may persist even in the absence of overt cardiometabolic disease.[15] In this context, assessing arterial stiffness in these groups, particularly those without clinically apparent cardiovascular disease, is essential for understanding whether hemodynamic regulation is affected in the early stages of COPD. Comparing arterial stiffness levels across different COPD subgroups may help demonstrate that cardiovascular risk is not limited to advanced disease but can also emerge in the early stages.

Pre-COPD and PRISm represent early at-risk states within the COPD spectrum and may already be associated with early systemic vascular alterations before overt airflow limitation becomes fully established. Although these conditions are conceptually distinct, both may reflect early respiratory impairment accompanied by smoking-related, inflammatory, and hemodynamic changes that could contribute to increased arterial stiffness. Evaluating arterial stiffness in this early-risk spectrum may therefore help clarify whether vascular involvement develops before advanced COPD.

In this context, the present study was designed to compare arterial stiffness across healthy controls, a combined pre-COPD/PRISm group, and different COPD stages, and to determine whether PWV is more strongly associated with spirometric severity or with age- and hemodynamic-related factors. We hypothesized that arterial stiffness would be higher across the early-risk and COPD spectrum than in healthy controls, that crude associations with respiratory impairment would be attenuated after adjustment for age and smoking exposure, and that hemodynamic parameters would remain independent determinants of PWV.

Materials and Methods

Study Design and Population

Participants were enrolled in the cross-sectional study at the Pulmonology Outpatient Clinic of Giresun Training and Research Hospital between June and November 2025. Using power analysis (G*Power),[16] with a type 1 error rate of 5%, a power of 95%, and a medium effect size (0.25), the minimum sample size required was 196 participants. The study population was ultimately categorized into four groups: healthy controls, a combined pre-COPD/PRISm group, early-stage COPD (GOLD A/B), and advanced COPD (GOLD E).[1] After application of the inclusion and exclusion criteria, a total of 241 participants, including 181 COPD patients and 60 healthy controls, formed the final study sample.

- Healthy controls: Individuals who underwent arterial stiffness measurement during a routine visit to the cardiology outpatient clinic and met the same age range and exclusion criteria as the patient groups. The healthy control group included individuals who visited the cardiology outpatient clinic for cardiovascular risk assessment but had no known cardiovascular disease, hypertension, diabetes, or dyslipidemia.
- Pre-COPD/PRISm group: Pre-COPD is defined as individuals with chronic respiratory symptoms but who do not yet meet the spirometric criteria for COPD diagnosis (FEV1/FVC <0.70).[13] PRISm (Preserved Ratio Impaired Spirometry) refers to individuals with spirometric FEV1 <80% but an FEV1/FVC ratio ≥0.70.[14] This heterogeneous structure reflects different pathophysiologies in the early stages.

- Early-stage COPD (GOLD A/B): FEV1/FVC <0.70, FEV1 ≥50%, mild-to-moderate symptoms (mMRC <2 and/or CAT score <10).[1]
- Advanced COPD (GOLD E): FEV1/FVC<0.70, FEV1<50%, moderate-severe symptoms (mMRC>2 and CAT score>10) or those with a history of two or more hospitalizations in the past year due to COPD.[1]

During the study recruitment period, 201 patients with COPD were recruited from the Chest Diseases Outpatient Clinic at Giresun Training and Research Hospital. Of these, 16 patients were excluded due to additional physical illnesses and comorbid chest pathologies (eg, asthma, interstitial lung disease, bronchiectasis, and lung malignancy), 12 patients due to inability to complete the spirometry test, five patients due to coronary artery disease, and four patients due to dyslipidemia diagnoses. The remaining 181 individuals and 60 healthy participants formed the final study sample. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024 guidelines, patients diagnosed with COPD by a pulmonologist were included as participants.[1] Disease severity was staged by a pulmonologist according to the expected percentage of FEV1 as per the GOLD 2024 guidelines, and the Modified Medical Research Council (mMRC) dyspnea scale and the COPD Assessment Test (CAT) were used to determine clinical severity.[1]

Inclusion Criteria: Participants must meet the study's group definitions, be between 18 and 65 years of age, and have no contraindications to participating in the study or to administering the scale. These inclusion criteria were applied uniformly across all study groups, including healthy controls and patient groups.

Exclusion Criteria: Individuals with acute infections or other systemic diseases, and those with major cardiometabolic diseases (eg, heart failure, coronary artery disease, uncontrolled hypertension, diabetes mellitus with complications, and chronic kidney disease) that could directly affect arterial stiffness, were excluded from the study.

The comorbidities included in the study were limited to conditions not known to have a direct and independent effect on arterial stiffness, based on existing literature, while conditions with established effects on vascular stiffness were excluded. The pre-COPD/PRISm group includes individuals who meet the PRISm definition and those who exhibit pre-COPD features without obstruction. Therefore, this group has a heterogeneous structure, and spirometric values show a wide distribution.

Data Collection Tools

Socio-demographic and Clinical Data Form: This form includes basic socio-demographic information such as age, gender, and occupation. Clinical data such as duration of COPD, smoking duration (pack-years), comorbidities, medications used, and number of exacerbations in the previous year are also recorded.

Spirometry: Spirometric parameters, including FEV_1 (% estimate), FVC (% estimate), and FEV_1/FVC (%), were obtained using a standard spirometer, and measurements were performed according to American Thoracic Society/ European Respiratory Society (ATS/ERS) guidelines.[17]

Modified Medical Resource Council (mMRC) Dyspnea Scale: mMRC is a 5-item scale developed by Bestall et al that assesses dyspnea severity.[18]

COPD Assessment Test (CAT): This 8-item test, scored 0–5, is recommended by GOLD to assess COPD symptoms.[1] The Turkish version, validated by Yorgancıoğlu et al, was used in the study.[19]

Arterial Stiffness Device: Arterial stiffness and cardiovascular hemodynamic parameters were assessed using the Mobil-O-Graph NG® device (IE.M. GmbH, Stolberg, Germany), a validated oscillometric system for noninvasive pulse wave analysis. The device was used to measure peripheral systolic and diastolic blood pressure, mean arterial pressure, pulse pressure, central pulse pressure, cardiac output, total peripheral resistance, augmentation pressure, reflection magnitude, and pulse wave velocity (PWV). The Mobil-O-Graph NG® system has been previously validated for the assessment of central hemodynamic parameters and pulse wave velocity using oscillometric pulse wave analysis methods.[20,21] PWV values obtained by Mobil-O-Graph represent the estimated aortic PWV derived from brachial oscillometric waveforms.

All measurements were performed in the morning under standardized conditions. Participants were seated comfortably and allowed to rest for at least 10 minutes before the measurement. An appropriately sized cuff was selected for each individual and placed on the upper arm. During the measurement, the cuff was automatically inflated to

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a suprasystolic pressure level to occlude the brachial artery transiently. Augmentation index (AI) and augmentation pressure (AP) were also derived from pulse wave analysis, and AI values were standardized to a heart rate of 75 bpm by the device software. Pressure waveforms generated by arterial pulsations were recorded by high-fidelity pressure sensors integrated into the cuff.

The recorded pulse waveforms were subsequently analyzed using the HMS Client Server software (Version 4.7.1®, IE.M. GmbH), which applies a validated transfer function to derive central hemodynamic parameters and arterial stiffness indices. The same trained operator obtained all measurements to minimize inter-observer variability.

Body surface area (BSA) was calculated using the Mosteller formula: BSA (m^2) = $\sqrt{[(\text{height (cm)} \times \text{weight (kg)}) / 3600]}$.

This study was approved by the Giresun Training and Research Hospital Scientific Research Ethics Committee (Decision No: 14.05.2025/25). Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the 2024 Helsinki Declaration.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). The normality of the data distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Numerical data were presented as mean ± standard deviation (SD) for normally distributed variables and as median (interquartile range, Q1–Q3) for non-normally distributed variables. Categorical variables were expressed as frequency and percentage (%).

For comparisons of numerical variables among multiple independent groups, one-way analysis of variance (ANOVA) was used for data satisfying the assumption of normal distribution, and the Kruskal–Wallis test was used for data not satisfying the assumption of normal distribution. Relationships between variables were evaluated using Pearson correlation and partial correlation analyses.

Clinical, functional, anthropometric, and hemodynamic variables that may be associated with PWV were pre-defined to represent different biological dimensions of arterial stiffness. Pearson correlation analyses were first applied to evaluate the relationships between PWV and these variables, followed by partial correlation analyses controlling for age and pack-years to account for potential confounding effects of age and smoking exposure.

Hierarchical linear regression analysis was used to examine the independent determinants of PWV. Regression models were constructed by adding age, mean arterial pressure (representing hemodynamic load), body surface area (an anthropometric variable), and FEV1% (reflecting COPD severity). The change in variance explained (ΔR^2) and the corresponding F-values of change statistics were reported for each model. Statistical significance was set at $p < 0.05$.

The reporting of this study was prepared per the recommendations of the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" guideline.[22]

Results

A total of 241 participants were included in the study. The age distribution showed an increasing trend across the groups. When gender distribution was examined, the proportion of female participants was higher in the healthy control group (n=36, 60%), whereas male participants were more prevalent in the COPD groups. This imbalance was considered a potential confounding factor and was accounted for in multivariate analyses. Significant differences were observed between the groups in sociodemographic variables ($p<0.05$ for all except smoking status), with increasing proportions of rural residence, lower education, and lower income across advancing COPD stages (Table 1). When smoking history was evaluated, it was observed that pack-year values increased with disease stage. Comorbidity prevalence was lowest in the healthy control group and highest in the COPD groups. In the present study, major cardiometabolic conditions known to directly affect arterial stiffness (eg, coronary artery disease, heart failure, uncontrolled hypertension, and diabetes with complications) were excluded. Therefore, the comorbidities observed in the sample mainly consisted of conditions with limited or no direct impact on arterial stiffness (eg, hypothyroidism, osteopenia, and allergic rhinitis). Height, weight, and body surface area were evaluated as anthropometric parameters; among these, body surface area was included in the multivariate models.

Table 1 Characteristics of Participants (N: 241)

Variable	Healthy Control (n=60)	Pre-COPD / PRISm (n=61)	COPD GOLD A/B (n=60)	COPD GOLD E (n=60)	P value
Age, years (mean ± SD)	62.00 ± 13.50	63.18 ± 10.41	65.88 ± 7.74	69.38 ± 9.44	<0.001
Sex, n (%)					<0.001
Female	36 (60.0)	17 (27.9)	10 (16.7)	7 (11.7)	
Male	24 (40.0)	44 (72.1)	50 (83.3)	53 (88.3)	
Place of residence, n (%)					<0.001
Urban	49 (81.7)	42 (68.9)	32 (53.3)	20 (50.0)	
Rural	11 (18.3)	19 (31.1)	28 (46.7)	30 (50.0)	
Marital status, n (%)					<0.039
Married	41 (68.3)	53 (86.9)	53 (88.3)	54 (80.0)	
Single	14 (23.3)	1 (1.6)	1 (1.7)	2 (3.3)	
Widowed / Divorced	5 (8.4)	7 (11.5)	6 (10.0)	4 (6.7)	
Educational level, n (%)					<0.001
No formal education	2 (3.4)	7 (11.5)	2 (3.3)	5 (8.3)	
Primary school	26 (43.3)	43 (70.5)	39 (65.0)	51 (85.0)	
High school	11 (18.3)	10 (16.4)	16 (26.7)	3 (5.0)	
University	21 (35.0)	1 (1.6)	3 (5.0)	1 (1.7)	
Employment status, n (%)					<0.001
Unemployed	25 (43.9)	13 (22.0)	6 (10.0)	9 (15.3)	
Employed	26 (45.6)	15 (25.4)	11 (18.3)	8 (13.6)	
Retired	6 (10.5)	31 (52.5)	43 (71.7)	42 (71.2)	
Financial Status, n (%)					<0.001
Low	11 (18.3)	25 (41.6)	25 (44.6)	37 (61.6)	
Middle	17 (28.3)	19 (31.6)	19 (32.1)	18 (30.0)	
High	32 (53.4)	16 (26.7)	14 (23.3)	5 (8.4)	
Smoking status, n (%)					0.357
Current smoker	25 (41.7)	35 (57.4)	32 (53.3)	30 (50.0)	
Former smoker	35 (58.3)	26 (42.6)	28 (46.7)	30 (50.0)	
Comorbidity (excluding major cardiometabolic diseases), n (%)					0.001
Yes	19 (31.7)	34 (55.7)	39 (65.0)	37 (61.7)	
No	41 (68.3)	27 (44.3)	21 (35.0)	23 (38.3)	
Pack-years, median (Q1–Q3)	14 (11–32.5)	34.5 (20–42.5)	40 (20–50)	42 (30–60)	0.571
mMRC score, median (Q1–Q3)	0 (0–1)	1 (0–2)	1 (0–2)	2 (1–3)	<0.001
CAT total score, median (Q1–Q3)	6 (3–10)	16 (12.5–20)	19 (14–24)	23 (18–29)	<0.001
FEV_1 (%predicted)	86.0 ± 15.54	84.4 ± 13.7	64.5 ± 9.0	40.5 ± 14.3	<0.001
FVC (%predicted)	81.7 ± 15.3	74.8 ± 15.6	61.1 ± 10.5	43.8 ± 14.1	<0.001

Notes: Data are presented as mean±standard deviation (SD) or number (%) unless otherwise indicated. Pack-years, mMRC, and CAT scores are presented as median (Q1–Q3). Percentages are calculated based on valid data. PRISm (preserved ratio impaired spirometry) refers to individuals with FEV_1 <80% predicted and FEV_1/FVC ≥0.70.
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV1%, forced expiratory volume in one second; FVC, forced vital capacity; PRISm, preserved ratio impaired spirometry.

When clinical symptoms were evaluated, mMRC and CAT scores, which reflect dyspnea severity and symptom burden, increased as the disease progressed. In spirometric evaluation, it was observed that FEV1 and FVC percentages were highest in the healthy control group and lowest in the COPD GOLD E group. Both FEV1 and FVC values showed a significant decrease with increasing COPD stage ($p<0.001$).

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No significant differences were found between the groups in terms of peripheral and central blood pressure parameters (p>0.05). However, heart rate differed significantly between the groups (p<0.001). Borderline low values were observed in the COPD GOLD E group in terms of total peripheral resistance (p=0.050). The lowest body surface area was found in the COPD GOLD E group (p=0.004).

PWV values were higher in the pre-COPD/PRISm, COPD GOLD A/B, and COPD GOLD E groups compared to healthy controls (p<0.001). The highest PWV values were found in the COPD GOLD E group. While no differences were observed between the groups in terms of augmentation pressure and reflection magnitude (p>0.05), the augmentation index showed a significant difference between the groups (p<0.001) (Table 2). Post-hoc comparisons indicated that PWV values in all patient groups were significantly higher than in healthy controls, and values in the COPD GOLD E group were significantly higher than those in both the pre-COPD/PRISm and COPD GOLD A/B groups.

All correlation and regression analyses were performed using the entire study population. Correlation analyses were performed to evaluate the relationships between PWV and clinical, functional, and hemodynamic variables before transitioning to multivariate models. In the raw analyses, PWV showed significant associations with FEV1%, FVC%, CAT, and mMRC scores (p<0.001 for all). Furthermore, PWV exhibited substantial positive correlations with mean arterial pressure and central pulse pressure. When age and pack-years were controlled for, the relationships between lung function and symptom scores and PWV weakened significantly and lost statistical significance. In contrast, the relationships between mean arterial pressure, central pulse pressure, and PWV persisted independently of age and smoking burden. The negative relationship between body surface area and PWV became statistically significant after controlling for age and pack-years (Table 3).

Table 2 Comparison of Arterial Stiffness and Hemodynamic Parameters Between Groups

	Healthy Control (HC) (n=60)	Pre-COPD / PRISm (n=61)	COPD (GOLD A/B) (n=60)	COPD (GOLD E) (n=60)	P value
Peripheral Blood Pressure					
pSBP (mmHg)	131.8 ± 19.9	131.6 ± 16.8	129.7 ± 18.4	129.1 ± 18.1	0.81
pDBP (mmHg)	86.3 ± 10.5	86.9 ± 11.7	85.8 ± 11.8	85.3 ± 12.6	0.87
MAP (mmHg)	107.1 ± 13.6	107.4 ± 12.7	105.9 ± 13.9	105.4 ± 13.9	0.81
HR (1/min)	91.9 ± 15.8[a]	81.6 ± 12.8[b]	81.5 ± 13.6[b]	86.7 ± 17.0[a,b]	**<0.001**
PP (mmHg)	45.6 ± 14.8	44.7 ± 13.4	43.9 ± 13.3	43.9 ± 13.3	0.90
Central / Hemodynamic Assessments					
cSBP (mmHg)	119.9 ± 18.1	120.6 ± 14.2	118.9 ± 16.0	118.4 ± 16.1	0.88
cDBP (mmHg)	88.0 ± 10.8	88.5 ± 11.9	86.9 ± 11.9	86.7 ± 11.7	0.81
cPP (mmHg)	31.9 ± 11.1	32.1 ± 9.4	31.9 ± 9.1	31.7 ± 10.7	0.99
CO (l/min)	4.98 ± 0.77	5.24 ± 0.77	5.18 ± 0.75	5.20 ± 0.76	0.24
TPR (s*mmHg/mL)	1.30 ± 0.14 [a]	1.24 ± 0.15[a,b]	1.24 ± 0.18[a,b]	1.22 ± 0.15[b]	0.050
CI (l/min*1/m^2)	2.76 ± 0.51	2.81 ± 0.49	2.76 ± 0.54	2.94 ± 0.48	0.162
BSA (m^2)	1.82 ± 0.18[a,b]	1.88 ± 0.17[a]	1.88 ± 0.19[a]	1.78 ± 0.19[b]	**0.004**
Arterial Stiffness & Wave Reflection Parameters					
AP (mmHg)	7.86 ± 5.04	6.37 ± 4.64	6.86 ± 5.23	7.18 ± 4.97	0.41
RM (%)	57.86 ± 8.97	60.18 ± 7.46	59.63 ± 8.99	60.28 ± 9.71	0.40
AI (%)	30.7 ± 10.6[a]	21.5 ± 11.9[b]	22.6 ± 11.7[b]	27.5 ± 13.3[a,b]	**<0.001**
PWV (m/s)	6.86 ± 1.63[a]	9.22 ± 1.70[b]	9.56 ± 1.28[b,c]	10.11 ± 1.71[c]	**<0.001**

Notes: PRISm refers to preserved ratio impaired spirometry (FEV1 <80% predicted and FEV1/FVC ≥0.70). Superscript letters (a, b, c) represent statistically homogeneous groups based on Tukey's post hoc comparisons. Groups sharing at least one letter are not significantly different, whereas those without a shared letter differ significantly (p < 0.05). Values are presented as mean±standard deviation (SD) or number (%) unless otherwise indicated. Bold values indicate statistical significance (p < 0.05).

Abbreviations: AI, Augmentation Index; AP, augmentation pressure; BSA, body surface area; cDBP, central diastolic blood pressure; CI, cardiac index; CO, cardiac output; COPD, Chronic Obstructive Pulmonary Disease; cPP, central pulse pressure; cSBP, central systolic blood pressure; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, heart rate; MAP, mean arterial pressure; pDBP, peripheral diastolic blood pressure; PP, pulse pressure; PRISm, Preserved Ratio Impaired Spirometry; pSBP, peripheral systolic blood pressure; PWV, pulse wave velocity; RM, reflection magnitude; TPR, total peripheral resistance.

Table 3 Correlations Between Pulse Wave Velocity and Clinical and Hemodynamic Variables

		Crude PWV Correlations	PWV (Age- and Pack-Year–Adjusted)
FEV1%	**r**	**−0.322**	0.116
	p	**<0.001**	0.082
FVC%	**r**	**−0.424**	0.053
	p	**<0.001**	0.429
CAT score	**r**	**0.457**	−0.056
	p	**<0.001**	0.403
mMRC score	**r**	**0.447**	0.125
	p	**<0.001**	0.061
BSA (m^2)	**r**	−0.102	**−0.160**
	p	0.115	**0.016**
MAP (mmHg)	**r**	**0.245**	**0.640**
	p	**<0.001**	**<0.001**
cPP (mmHg)	**r**	**0.363**	**0.637**
	p	**<0.001**	**<0.001**

Notes: Crude correlations were assessed using Pearson correlation analysis. Age- and pack-year–adjusted correlations were calculated using partial correlation analysis. Bold values indicate statistical significance ($p < 0.05$).
Abbreviations: PWV, pulse wave velocity; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; CAT, COPD Assessment Test; mMRC, modified Medical Research Council dyspnea scale; BSA, body surface area; MAP, mean arterial pressure; cPP, central pulse pressure.

Table 4 Hierarchical Linear Regression Models Predicting Pulse Wave Velocity (PWV)

Predictor	Model 1 B±SE	Model 2 B±SE	Model 3 B±SE	Model 4 B±SE
Constant	1.399 ± 0.199 ***	−2.390 ± 0.324 ***	−1.113 ± 0.461 *	−1.272 ± 0.471 **
Age (years)	0.125 ± 0.003 ***	0.125 ± 0.002 ***	0.125 ± 0.002 ***	0.127 ± 0.003 ***
MAP	–	0.036 ± 0.003 ***	0.036 ± 0.003 ***	0.035 ± 0.003 ***
BSA	–	–	−0.700 ± 0.184 ***	−0.735 ± 0.185 ***
FEV1%	–	–	–	0.003 ± 0.002 (p=0.115)

Notes: Model fit/change: Model 1: $R^2 = 0.865$, Model 2: $R^2 = 0.922$, $\Delta R^2 = 0.057$, $p<0.001$, Model 3: $R^2 = 0.927$, $\Delta R^2 = 0.004$, $p<0.001$, Model 4: $R^2 = 0.927$, $\Delta R^2 = 0.001$, $p = 0.115$. Durbin–Watson: 1.830. Significance: * $p<0.05$, ** $p<0.01$, *** $p<0.001$.
Abbreviations: B, unstandardized regression coefficient; SE, standard error; MAP, mean arterial pressure; BSA, body surface area; PWV, pulse wave velocity; FEV1, forced expiratory volume in one second.

In hierarchical linear regression analysis, age was identified as the variable showing the strongest association with PWV ($\beta=0.94$; $p<0.001$). Adding mean arterial pressure to the model significantly increased the explained variance ($\Delta R^2 = 0.057$; $p < 0.001$). Body surface area was found to be independently and negatively associated with PWV ($\beta=-0.07$; $p<0.001$), while adding FEV1% to the model did not contribute significantly to the model ($\Delta R^2=0.001$; $p=0.115$) (Table 4).

Discussion

In this study, PWV was found to increase in all COPD groups, consistent with the literature.[14,23] This increase was most significant in GOLD E, which represents severe COPD. It was also determined that PWV increased in the pre-COPD/PRISm group compared to the healthy group. An essential finding of this study is that although peripheral and central blood pressure values were broadly similar across groups, significant differences were observed in arterial stiffness and wave reflection parameters. In this respect, the study shows that vascular and hemodynamic changes can occur in the early stages, independent of pressure levels. Apart from PWV, the augmentation index also differed between groups. When compared with reference

PWV values reported in population-based studies, the relatively lower PWV observed in our healthy control group may be explained by the strict exclusion of individuals with cardiometabolic comorbidities, the use of oscillometric estimation rather than direct carotid–femoral measurement, and potential sample-specific characteristics.

Studies examining arterial stiffness in COPD have consistently reported increased PWV, suggesting elevated cardiovascular risk.[23] In line with these findings, our study also demonstrates increased arterial stiffness, particularly in advanced COPD. In our study, PWV increased significantly in the pre-COPD/PRISm group, while MAP and cPP levels were similar between groups; however, the relationship between MAP, cPP, and PWV remained strong, independent of age and smoking burden. These groups constitute patients who do not yet meet the COPD diagnostic criteria. Therefore, it can be considered that the cardiovascular risk profile may be adversely affected in these groups even before a clinical diagnosis of COPD is made. This finding is consistent with large-scale cohort studies showing an increased risk of cardiovascular events and mortality in the PRISm phenotype.[14,24] Studies have reported an increase in PWV in PRISm groups in regression analyses, independent of cardiovascular risk factors, findings similar to ours, but the underlying mechanism remains unknown.[14,15,24,25] In our study, major cardiometabolic conditions such as diabetes mellitus were excluded, which may explain differences from previous studies reporting higher comorbidity burden. Previous studies have reported a higher prevalence of cardiovascular diseases and diabetes mellitus in PRISm populations; however, these conditions were excluded in our study, which may explain differences between our findings and the existing literature.[15,25] Excluding comorbidities that could affect arterial stiffness in our study may yield a more homogeneous group.

In our study, the cPP and MAP changes observed in the pre-COPD/PRISm group suggest that not only arterial stiffness but also vascular-load interaction may be impaired in pre-COPD/PRISm. Indeed, one study suggested that cardiovascular risk in PRISm is associated not with an increase in PWV per se, but with decreased left ventricular stroke volume, which may lead to increased cardiac load and a future risk of heart failure.[26] The literature indicates that studies examining these groups remain limited.

Studies have shown that systemic inflammation begins early in the course of COPD. In addition, increased oxidative stress due to exogenous exposures is observed in COPD. This inflammatory response can lead to endothelial dysfunction through oxidative stress.[27–29] Endothelial dysfunction may impair perception of hemodynamic load.[23] Consequently, arterial stiffness may develop, affecting the vascular wall, elasticity, and transmission of blood pressure waves. In COPD, structural abnormalities that cause permanent lung obstruction are caused by external exposures. However, given patients' exposures, it is thought that vascular effects may occur even before spirometric values deteriorate. Indeed, studies have shown that cardiovascular and endocrinological diseases and conditions, such as obesity, are associated with PRISm groups.[30,31] This may be the mechanism underlying the impaired arterial stiffness parameters observed in the pre-COPD/PRISm group in our study.

In our study, we observed that a change in augmentation pressure did not accompany the increase in PWV in the COPD and pre-COPD/PRISm groups. However, the augmentation index was low in the early stage and increased in the advanced stage. This situation may suggest that hemodynamic adaptation mechanisms come into play as the severity of the disease increases and the timing of wave reflection changes.[32,33] Consequently, it may suggest a silent hemodynamic reorganization in the early stage. However, the cross-sectional nature of the study limits the ability to determine cause-and-effect relationships. Importantly, PWV and AI reflect different physiological aspects of arterial function. While PWV represents structural arterial stiffness, AI is influenced by wave reflection, heart rate, and peripheral vascular resistance. Therefore, the observed increase in PWV without a parallel increase in AI in early stages may reflect early structural vascular changes before significant alterations in wave reflection dynamics occur.

Analyses revealed that spirometric parameters and COPD symptom scores correlated with PWV. However, when age and smoking were controlled for, this relationship disappeared. Conversely, the relationship between MAP and cPP persisted and even increased. These findings suggest that arterial stiffness in early stages of COPD may be more strongly driven by hemodynamic load than by spirometric impairment.[34]

The literature has also identified an increase in extrapulmonary pathologies, as well as the development of PRISm associated with exogenous exposures.[30] Therefore, it may be considered that individuals diagnosed with PRISm should be monitored not only from a pulmonary perspective but also in terms of their cardiovascular risk profile. There are many studies suggesting that PWV can predict cardiovascular risks in COPD.[3,10] However, as seen in the multiple regression model, the reason explaining PWV, especially in the early stages, is hemodynamic load rather than spirometric abnormalities. The disease disrupts hemodynamics without causing pulmonary obstruction. For these reasons, PWV measurement may be recommended as an early risk indicator in the future. However, PWV measurement alone is not sufficient for screening and treatment recommendations. Although PWV indicates vascular aging, the Asian expert consensus recommends that extensive randomized studies are needed to determine the benefit of treatment strategies based on PWV.[35]

The inclusion of pre-COPD patients in addition to PRISm, the moderate sample size, and the use of standardized devices by a single technician are among the study's strengths. Furthermore, multivariate analyses clearly identified the factors affecting PWV. Considering PWV within a multidimensional hemodynamic framework alongside MAP, cPP, and HR may contribute to a better understanding of the underlying mechanisms. However, the single-center, cross-sectional design of the study prevents the determination of causality and the generation of generalizable results. Another limitation is the heterogeneity of the PRISm and pre-COPD groups. The fact that both groups developed similar exposures may have contributed to the meaningful outcome. The device used to perform an estimated aortic PWV measurement also yielded arterial stiffness measurements based on indirect data. However, the device's mobility and applicability across multiple centers are valuable for future studies and screenings. Another important limitation is the imbalance in age and sex distribution between groups, which may affect group comparisons despite adjustment in multivariate analyses.

Conclusion

Arterial stiffness findings previously demonstrated in advanced stages of COPD are also observed in early stages of COPD and even in pre-COPD and PRISm conditions. In pre-COPD and PRISm conditions, arterial stiffness may emerge as part of hemodynamic remodeling. These findings suggest that, in the early stages of COPD and in pre-COPD/PRISm conditions, not only is arterial structural stiffness increased, but the hemodynamic system is also affected. Although the underlying mechanisms remain unclear, these findings suggest that early hemodynamic alterations may precede overt airflow limitation. Further prospective studies on pre-COPD and PRISm are needed.

Use of AI for Writing Assistance

Artificial intelligence (AI)-enabled technologies, such as large language models (LLMs), chatbots, or image generators, were not used in this article.

Abbreviations

AI, Augmentation Index; AP, Augmentation Pressure; BSA, Body Surface Area; CAT, COPD Assessment Test; CDBP, Central Diastolic Blood Pressure; CI, Cardiac İndex; CO, Cardiac Output; COPD, Chronic Obstructive Pulmonary Disease; CPP, Central Pulse Pressure; CSBP, Central Systolic Blood Pressure; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, Heart Rate; MAP, Mean Arterial Pressure; mMRC, Modified Medical Research Council; PDBP, Peripheral Diastolic Blood Pressure; PP, Pulse Pressure; PRISm, Preserved Ratio Impaired Spirometry; PSBP, Peripheral Systolic Blood Pressure; PWV, Pulse Wave Velocity; RM, Reflection Magnitude; TPR, Total Peripheral Resistance.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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 declare no conflicts of interest in this work.

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