Arterial stiffness in patients with COPD: the role of systemic inflammation and the effects of pulmonary rehabilitation

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ABSTRACT Clear evidence for an association between systemic inflammation and increased arterial stiffness in patients with chronic obstructive pulmonary disease (COPD) is lacking. Moreover, the effects of pulmonary rehabilitation on arterial stiffness are not well studied.

We aimed to 1) confirm increased arterial stiffness in COPD; 2) evaluate its correlates including systemic inflammation; and 3) study whether or not it is influenced by pulmonary rehabilitation.

Aortic pulse-wave velocity (APWV) was determined in 168 healthy volunteers, and APWV and inflammatory markers were determined in 162 COPD patients during baseline evaluation of a pulmonary rehabilitation programme. A complete post-pulmonary rehabilitation dataset was collected in 129 patients.

It was found that APWV was increased in COPD patients when compared with controls, blood pressure and age predicted baseline APWV, and systemic inflammatory markers were not independently related to APWV. Although baseline APWV was predictive for the change in APWV after pulmonary rehabilitation ($r = -0.77$), on average APWV did not change (10.7 ± 2.7 *versus* 10.9 ± 2.5 $m \cdot s^{-1}$; $p = 0.339$).

Arterial stiffness in COPD is not related to systemic inflammation and does not respond to state-of-the-art pulmonary rehabilitation. These results emphasise the complexity of cardiovascular risk and its management in COPD.

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Introduction

Chronic obstructive pulmonary disease (COPD) is considered a complex and heterogeneous condition affecting multiple organ systems [1]. Indeed, cardiovascular disease is a major cause of death in COPD [2, 3]. Persistent low-grade systemic inflammation has been suggested as the pathophysiological link between both diseases [4], but evidence is lacking.

Aortic pulse wave velocity (APWV), considered to be the gold standard for measuring central arterial stiffness [5], is an independent predictor of cardiovascular events and mortality [6] and is increased in patients with COPD [7, 8]. Arterial stiffness has been positively associated with levels of different systemic inflammatory markers in healthy individuals [9] and different patient populations [10, 11]. One COPD study showed weak correlations with interleukin (IL)-6 and soluble tumour necrosis factor receptor 1 (sTNFR1), but not with sTNFR2 [7].

Exercise-based pulmonary rehabilitation (PR) seems to have a beneficial effect on arterial stiffness in patients with COPD [12, 13]. However, these results need to be confirmed in larger samples.

We sought to confirm increased arterial stiffness in patients with COPD referred for PR and to evaluate its determinants, including systemic inflammation. Moreover, we aimed to prospectively study the impact of a state-of-the-art PR programme on APWV and other functional vascular outcomes.

Methods

Study design and subjects

The CIRO comorbidity (CIROCO) study (approved by the local ethics and review boards (MEC 10-3-067)) was a 2-year prospective single-centre study. Patients with COPD were recruited at the start of PR at CIRO+ (Centre of Expertise for Chronic Organ Failure, Horn, the Nethrlands). Study design, inclusion and exclusion criteria and details of the assessments have been published [14]. Briefly, in addition to comprehensive pre- and post-PR clinical assessment, patient's haemodynamic status was assessed: blood pressure, pulse pressure, pulse wave analysis and APWV (SphygmoCor; AtCor Medical, Sydney, Australia). APWV was measured by recording ECG-gated carotid and femoral artery waveforms. The Sphygmocor system software assured the quality of the pulse wave measurement. A detailed screen showed 10 s of recorded and analysed waveforms, which can be examined to assess overall consistency of the waveforms. In addition, a detailed report helped to interpret the consistency of the waveforms during the 10-s measurement. A measurement was only retained when it met the predefined quality thresholds. After marking the exact location, measurements were repeated three times to secure reproducibility. A measurement was accepted when it was reproducible three times with minimal variation, as judged by the biomedical technologist. The retained APWV measurement was the mean of the three measurements.

Shortest distances from manubrium to the marked location on the femoral artery (*via* the navel) were measured. Wave transit time was calculated by the system software, using the R-wave of the simultaneously recording ECG as a reference frame. APWV was determined by dividing the distance between the two recording sites by the wave transit time. For baseline comparison, healthy never, former and current-healthy elderly smokers without airflow limitation underwent lung function tests and haemodynamic assessments as part of the ICE-AGING (Individualized COPD Evaluation in relation to AGEing) study (MEC 10-3-033).

PR programme

CIRO+ provides a state-of-the-art interdisciplinary PR programme for patients with COPD consisting of 40 sessions, in line with the latest official American Thoracic Society and European Respiratory Society statement on PR [15]. During the baseline assessment a careful characterisation of the extrapulmonary features and comorbidities of patients with COPD were performed, which determined the application of various treatments: physical exercise training, occupational therapy, dietary counselling, psychosocial counselling, education and exacerbation management. Physical exercise training was the cornerstone of the programme, consisting of exercises to strengthen groups of muscle in the upper and lower extremities, treadmill walking and stationary cycling. All exercises were performed at moderate to high intensity to obtain an overload stimulus. Moreover, the training intensity increased during the rehabilitation period, based on dyspnoea and fatigue symptom scores. All patients underwent flexibility exercises, general physical exercise for lower and upper extremities, and daily supervised 30-min outdoor walks.

Statistical analysis

Statistics were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Results are expressed as mean$\pm$SD or count (%). For comparison, Chi-squared tests, independent samples t-test, paired t-test or ANOVA were used where applicable. Relationships between continuous variables were analysed using simple and/or multivariate linear regression. Figure 1 was obtained using SAS version 9.1 (SAS Institute

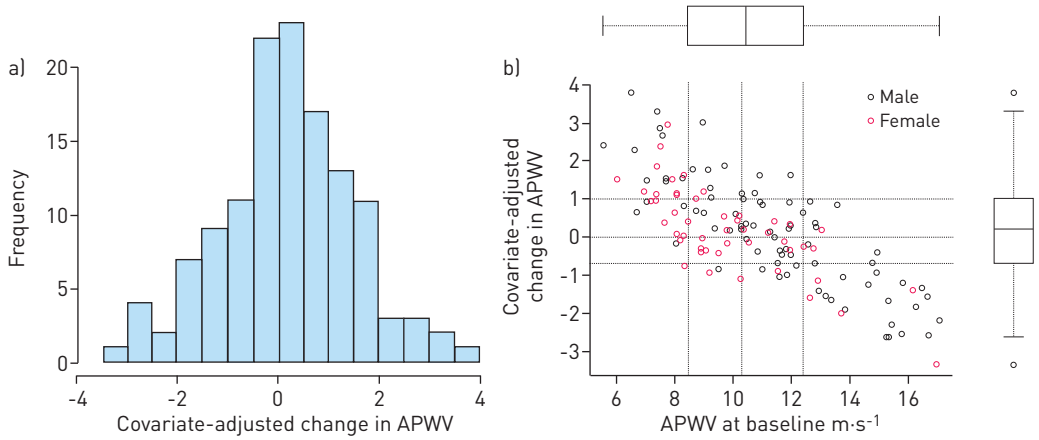

FIGURE 1 Covariate-adjusted change in aortic pulse wave velocity (APWV) after pulmonary rehabilitation (PR) in function of baseline APWV level. Change in APWV is adjusted for age, mean blood pressure, sex and body mass index. a) shows the distribution of the change in APWV after PR. b) shows the change in APWV after PR in function of the baseline APWV level for males and females. Correlation: r= -0.77; p<0.001.

Inc., Cary, NC, USA). More precisely, a model was constructed for change in APWV including the covariates: sex, age, body mass index (BMI), mean blood pressure, and APWV at baseline. Only fixed effects were used, as baseline APWV was included as a covariate and only two time-points were observed. Males aged 60 years with a BMI of 25 $kg \cdot m^{-2}$, mean blood pressure of 100 mmHg, and a baseline APWV level of 10 $m \cdot s^{-1}$ were the reference group. All p-values <0.05 were considered statistically significant.

Results

Subjects

Of 255 prospectively recruited patients, 42 (16.5%) were ineligible (online supplementary fig. e1). 51 (23.9%) of the 213 eligible COPD patients were excluded because of unsuccessful APWV measurements at baseline. Patients with unsuccessful APWV measurements had a significantly higher BMI, fat-free mass index (FFMI), triglycerides, glucose, diffusing capacity of the lung for carbon monoxide (*D*LCO), and estimated glomerular filtration rate compared with those with successful measurements (online supplementary table e1). A total of 162 subjects with successful baseline assessment started PR. Of these, nine (5.6%) subjects dropped out from the study before the end of the PR programme (online supplementary fig. e1). In 24 (15.7%) subjects, APWV measurements failed following PR. These subjects did not significantly differ from subjects with two successful APWV measurements in terms of baseline characteristics and PR outcome. Therefore, 129 patients with COPD had full data before and after PR.

Baseline characteristics

On average, the study sample consisted of older patients with a substantial smoking history, moderate-to-severe COPD, and impaired diffusion capacity, but normal arterial blood gases (table 1). Almost one-third of the patients were active smokers, while 14% of the patients were on long-term oxygen therapy. Patients generally had normal BMI and FFMI. Most patients reported a necessity to stop while walking at their own pace.

About one-third of the patients had self-reported cardiovascular comorbidity. Subjects generally had a high normal blood pressure and resting heart rate. Other baseline measurements and inflammatory biomarkers are shown in table 1.

The majority of the patients used long-acting anticholinergics and/or combined inhaled corticosteroids and long-acting β-agonists (online supplementary tables e2 and e3). Moreover, ~40% of the patients used one or more blood pressure lowering drugs and almost 35% used lipid lowering drugs.

Characteristics of the healthy controls, stratified for smoking history are also shown in table 1. These healthy-control subjects are slightly younger and had slightly higher BMI and FFMI when compared with the patients with COPD. As, by definition, pulmonary function is normal in these subjects, these subjects used less antihypertensive medication and fewer anxiolytics, antidepressives, calcium supplementation, bisphosphonates or antacids when compared with the COPD patients (online supplementary table e3).

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TABLE 1 Baseline characteristics of subjects with chronic obstructive pulmonary disease (COPD) and non-COPD controls

	COPD	Never-smoking controls	Ex-smoking controls
Subjects	162	65	102
Demographics			
Age years	63.8±6.9	57.9±8.1*	61.4±6.7*,#
Male	97 (59.9)	31 (47.0)*	47 (45.6)*
Active smoker	47 (29.0)	0	0
Long-term oxygen therapy	22 (13.6)	0	0
Smoking history pack-years	45.9±27.3	0±0	15.4±14.4*
Body composition			
Body mass index kg·m^{-2}	25.0±4.1	26.7±3.9*	27.6±3.8*
Fat-free mass index kg·m^{-2}	16.6±2.1	17.6±2.4*	17.9±2.4*
Bone mineral density T-score	-1.1±1.3		
Pulmonary function			
FEV1 L	1.40±0.55	3.4±0.9*	3.3±0.9*
FEV1 % predicted	51.4±17.4	119.6±14.8*	119.2±17.7*
FEV1/FVC %	39.5±11.1	78.0±5.0*	78.0±8.4*
*D*LCO % predicted	53.8±16.7	95.8±12.3*	91.7±17.7*
Blood gases			
P_{aCO_2} kPa	5.3±0.6		
P_{aO_2} kPa	9.5±1.1		
Oxygen saturation %	94.4±7.6		
Functional outcome			
6MWD m	475±108		
CWRT time s	359±284		
Leg press weight kg	101±47		
mMRC grade	2.1±1.1		
SGRQ points	51.6±18.4		
Charlson comorbidity index	1.57±0.89		
Myocardial infarction	16 (9.9)		
Heart failure	5 (3.1)		
Peripheral arterial disease	30 (18.5)		
Cerebrovascular disease	14 (8.6)		
Any cardiovascular disease	50 (30.9)		
Diabetes	7 (4.3)		
Clinical chemistry			
Triglycerides mmol·L^{-1}	1.5±0.7		
Low-density lipoprotein mmol·L^{-1}	2.9±1.0		
High-density lipoprotein mmol·L^{-1}	1.7±0.5		
Glucose mmol·L^{-1}	5.7±0.7		
Creatinine	87.5±22.6		
eGFR mL·min^{-1}	75.9±21.5		
Systemic inflammatory markers			
C-reactive protein mg·L^{-1}	4.6±6.1		
Interleukin-6 pg·mL^{-1}	3.3±4.5		
Interleukin-8 pg·mL^{-1}	13.0±5.3		
sTNFR1 pg·mL^{-1}	2186±771		
sTNFR2 pg·mL^{-1}	3714±1435		
Leukocytes 10^9 per L	7.5±2.0		

Data are presented as n, mean±SD or n (%). FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide; P_{aCO_2}: arterial carbon dioxide tension; P_{aO_2}; arterial oxygen tension; 6MWD: 6-min walking distance; CWRT: continuous work rate test; mMRC: modified Medical Research Council; SGRQ: St George's Respiratory Questionnaire; eGFR: estimated glomerular filtration rate; sTNFR: soluble tumour necrosis factor receptor. *: $p<0.05$ in comparison with subjects with COPD; #: $p<0.05$ in comparison with never-smoking controls.

Haemodynamic measurement in COPD patients and healthy controls

Patients with COPD had a significantly higher APWV compared with never smoking and ex-smoking controls (table 2). Consistently, central augmentation index (normalised for a heart rate of 75 beats per

TABLE 2 Haemodynamic measurements at baseline of subjects with chronic obstructive pulmonary disease (COPD) and controls

Haemodynamic measurements	COPD	Never-smoking controls	Ex-smoking controls
Subjects n	162	65	102
Aortic pulse wave velocity m·s^{-1}	10.9±2.8	8.7±2.2*	9.0±2.9*
Central augmentation index %	31.2±8.6	24.6±8.1*	26.7±9.4*
Peripheral mmHg			
Systolic pressure	137±21	141±17	146±21*
Diastolic pressure	82±10	84±8	85±9*
Mean pressure	102±13	105±11	108±13*
Pulse pressure	55±16	57±13	61±16*
Cardiac frequency beats per min	68±11	58±8*	59±8*
Central pressure mmHg			
Systolic pressure	129±20	133±16	138±21*
Diastolic pressure	83±10	85±9	86±9*
Mean pressure	102±13	105±11	108±13*
Pulse pressure	46±15	48±12	52±15*

Data are presented as mean+SD, unless otherwise stated. *: $p<0.05$ in comparison with subjects with COPD.

min) was higher in subjects with COPD compared with both control groups. Ex-smoking controls had a higher peripheral and central blood pressure compared with COPD patients. Although peripheral pulse pressure is higher in ex-smoking controls, central pulse pressure is higher in COPD patients. COPD patients have a significantly higher heart rate compared with both control groups (table 2).

Determinants of APWV in COPD

APWV did not correlate with systemic levels of leukocytes, C-reactive protein (CRP), IL)-6, IL-8 or sTNFR2. A weak but statistically significant correlation was found between APWV and sTNFR1. After adjusting for age, mean blood pressure, sex and BMI none of the systemic inflammatory markers were associated with APWV (table 3). Moreover, in a multivariate, backward linear-regression model, including all assessed demographics and clinical variables, only blood pressure ($\beta=0.380$, t-test=4.515; $p<0.001$) and age ($\beta=0.376$, t-test=3.283; $p=0.001$) were independently associated with APWV. The systemic inflammatory markers, as well as *D*LCO, forced expiratory volume in 1 s % predicted, bone mineral density T-score, BMI, lipids, blood glucose, renal function and smoking status did not explain the variance in baseline APWV in patients with COPD (online supplementary table e4).

Effects of PR

The following parameters all improved significantly when compared with baseline: 6-min walking distance (from 478±108 to 509±102 m), cycle endurance (from 371±275 to 569±396 s), muscle strength (leg press, from 103±48 to 128±50 kg), health status (St George's Respiratory Questionnaire, from 52.0±19.9 to 48.2±18.7 points) and dyspnoea grade (modified Medical Research Council grade 2.14±1.2 to

TABLE 3 Simple and multivariate linear regression with aortic pulse wave velocity as the dependent variable

	Simple linear regression			Multivariate linear regression[#]			
	β	t-test	p-value	β	t-test	p-value	F-test change of the model[¶]
C-reative protein ng·mL^{-1}	0.134	1.584	0.116	0.098	1.325	0.187	-6.044
Interleukin-6 pg·mL^{-1}	0.065	0.761	0.448	0.017	0.231	0.818	-6.477
Interleukin-8 pg·mL^{-1}	0.101	1.192	0.235	0.101	1.357	0.177	-6.165
sTNFR1 pg·mL^{-1}	0.171	2.034	0.044	0.064	0.791	0.430	-6.373
sTNFR2 pg·mL^{-1}	0.126	1.488	0.139	-0.013	-0.165	0.869	-6.472
Leukocytes ×10^{9} per L	0.043	0.547	0.585	0.022	0.327	0.744	-3.185

sTNFR: soluble tumour necrosis factor receptor. [#]: adjusting for age, mean blood pressure, sex and body mass index (BMI); [¶]: F of the model with age, mean blood pressure, sex and BMI=15.66.

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1.54±1.0 points) (online supplementary table e5). BMI did not change after PR in overweight and obese patients (n=65, 28.5±2.6 *versus* 28.5±2.7 kg·m^{-2}; p=0.744). In underweight patients (n=23), BMI increased significantly (18.7±1.5 *versus* 19.4±1.3 kg·m^{-2}; p<0.001). The systemic inflammatory markers, lipids, fasting glucose and leukocytes did not change following PR (online supplementary table e6).

APWV, central or peripheral blood pressure, or augmentation index did not change following PR, while peripheral- and central-pulse pressure increased (fig. 2). A statistically significant, but most probably clinically irrelevant, reduction in cardiac frequency was seen (table 4). Also, after stratification of the study sample in different relevant subgroups, no changes in APWV were noticed after PR (table 5).

The change in APWV following PR was negatively correlated (r= -0.77, p<0.001) with the level of APWV at baseline, after adjustment for baseline age, average blood pressure, sex and BMI in a linear fixed effects model (fig. 1). Interestingly, subjects with a low baseline APWV (<8 m·s^{-1} (25th percentile of the study sample)) whose APWV values increased by at least 0.5 m·s^{-1} after PR (n=19) and patients with a high baseline APWV (12.5 m·s^{-1} (75th percentile of the study sample)) whose APWV values decreased at least 0.5 m·s^{-1} (n=15) were not different with respect to baseline clinical characteristics, systemic inflammation or PR outcome.

Discussion

The main findings of this study are as follows. First, central arterial stiffness is increased in a large sample of subjects with COPD compared with healthy controls, and variance in arterial stiffness is partially determined by age and resting blood pressure. Secondly, markers of systemic inflammation do not explain the variance in arterial stiffness in COPD. Thirdly, although patients with COPD improved on conventional rehabilitation outcomes, arterial stiffness generally does not change following PR.

Arterial stiffness in COPD

Cardiovascular disease is common in patients with COPD and affects prognosis [16]. Moreover, patients with COPD have stiffer arteries compared with healthy control subjects [7, 17]. The current study corroborates these findings. Surprisingly, blood pressure and pulse pressure were higher in ex-smoking controls. This is probably due to less use of antihypertensive therapy in healthy subjects.

Arterial stiffness has been proposed as a mechanistic link between COPD and cardiovascular disease [18]. Increasing arterial stiffness alters arterial pressure and flow dynamics and impacts cardiac performance and coronary perfusion with consequent cardiovascular disease [19]. Arterial stiffness is thought to be the result of a remodelling process with elastin fragmentation and collagen replacement in the extracellular matrix [19]. A systemic susceptibility to lung, skin and arterial degradation of elastin and extracellular matrix remodelling has been suggested in patients with an emphysematous phenotype of COPD [20]. Indeed, McAllister *et al.* [21] showed a positive correlation between arterial stiffness and high-resolution computed tomography (HRCT)-quantified emphysema in 77 COPD patients. HRCT was not available in

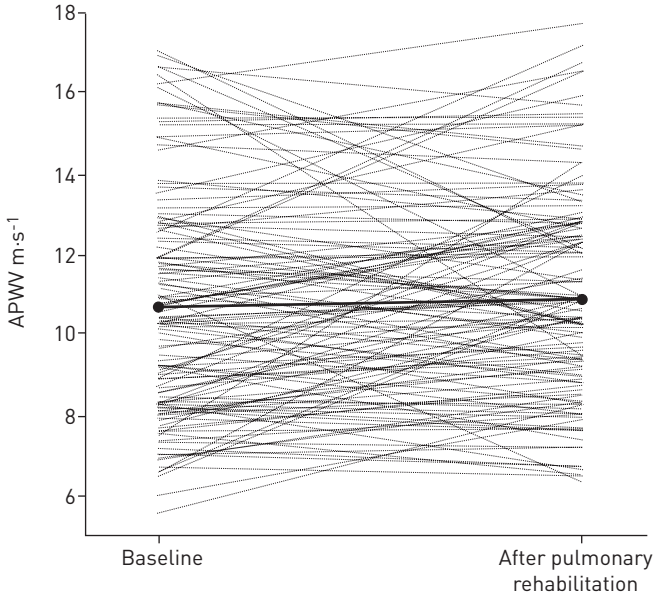

FIGURE 2 Data plot for aortic pulse wave velocity (APWV) in each patient before and after pulmonary rehabilitation. Circles and solid line represent the mean.

TABLE 4 Differences in aortic pulse wave velocity and other haemodynamics in subjects who completed pulmonary rehabilitation (PR)[#]

Haemodymanic measurement	Baseline	After PR	p-value
Aortic pulse wave velocity m·s^{-1}	10.7±2.7	10.9±2.5	0.339
Central augmentation index %	30.8±8.1	30.2±8.1	0.129
Peripheral pressure mmHg			
Systolic pressure	135±19	137±19	0.064
Diastolic pressure	81±9	81±9	0.377
Mean pressure	101±12	101±12	0.427
Pulse pressure	54±15	57±15	0.004
Cardiac frequency beats per min	68±11	67±11	0.032
Central pressure mmHg			
Systolic pressure	127±18	129±19	0.061
Diastolic pressure	82±9	82±9	0.386
Mean pressure	101±12	101±12	0.428
Pulse pressure	44±14	47±14	0.003

Data are presented as mean±SD, unless otherwise stated. [#]: n=129.

our study, but *D*LCO (as another surrogate for pulmonary emphysema) was not associated with APWV. Although *D*LCO and computed tomography-quantified emphysema have shown to be only moderately correlated [22], the discrepancy in these surrogates for pulmonary emphysema is intriguing as the populations in both studies are quite similar regarding demographics and clinical characteristics.

Also, vascular calcification may have a role in arterial stiffness in COPD, as it is inversely associated with bone mineral density in the general population [23], and osteoporosis is highly prevalent in COPD. Indeed, SABIT *et al.* [7] showed the highest arterial stiffness in nine emphysematous patients with osteoporosis at the hip, compared with 62 emphysematous subjects without osteoporosis. However, these differences were not found for the 13 subjects with osteoporosis of the spine and total T-score was not reported in that study.

In contrast, in the present study, total body bone mineral density T-score did not independently predict APWV, suggesting that this association might be more complex than assumed at present. Moreover, multivariate analysis indicated only increasing age and higher blood pressure to be independent predictors of increased arterial stiffness. This is comparable to the general population and multiple other patients groups, as was recently systematically reviewed [24].

Arterial stiffness and systemic inflammation

Increased levels of systemic inflammatory markers (leukocytes, CRP, tumour necrosis factor-α, IL-6 and IL-8) have been reported in COPD [25], and several of these have been associated with subclinical

TABLE 5 Difference in aortic pulse wave velocity (APWV) after pulmonary rehabilitation (PR) in different subgroups

	Subjects n	APWV baseline	APWV after PR	p-value
Overweight and obese	65	10.9±2.7	11.2±2.3	0.315
Underweight	23	10.3±2.8	10.4±3.2	0.830
No blood pressure lowering medication	79	10.5±2.6	10.7±2.4	0.383
No lipid lowering drugs	92	10.5±2.7	10.7±2.4	0.209
No cardiovascular medical history according to the CCI	60	10.3±2.6	10.6±2.5	0.232
No blood pressure lowering medication and no lipid lowering drugs	69	10.4±2.7	10.7±2.5	0.340
Active smokers	35	10.5±2.9	10.3±2.5	0.593
Ex-smokers	94	10.8±2.7	11.1±2.5	0.151
Male	80	11.2±2.8	11.5±2.7	0.520
Female	49	9.8±2.4	10.0±1.8	0.417
Improvement of >50 m in 6MWD and >4 points on SGRQ	25	10.4±2.7	10.4±1.9	0.954
Normal blood pressure <140/90 mmHg	79	10.0±2.5	10.2±2.4	0.395
Hypertensive >140/90 mmHg	49	11.8±2.7	12.0±2.3	0.585

Data are presented as mean±SD, unless otherwise stated. CCI: Charlson comorbidity index; 6MWD: 6-min walking distance; SGRQ: St George's Respiratory Questionnaire.

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atherosclerosis [26] and ischaemic heart disease [27]. Similar to SABIT *et al.* [7], we found a univariate association between APWV and sTNFR1, but we could not confirm the association with IL-6. However, IL-6 was reported to be significantly associated with APWV in a multivariate regression; although this needs to be interpreted with caution, as the control subjects were also included in the regression analysis. In our study, the multivariate model only included patients with COPD.

Systemic inflammation is thought to accelerate and stimulate the vascular extracellular matrix remodelling process of elastin fragmentation and collagen deposition, resulting in arterial stiffness [19]. However, evidence for a causal relationship between low-grade systemic inflammation and a high incidence of cardiovascular disease in COPD is lacking. In addition, studies showed comparable circulating levels of inflammatory biomarkers in COPD patients with and without cardiovascular disease [28]. Furthermore, it was recently shown that systemic inflammation does not affect all patients with COPD. Only 16% of patients in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort had long-term systemic inflammation, while one-third of the patients in this cohort did not have systemic inflammation at all during a 1-year follow-up [29]. Interestingly, increasing age and having an overweight to obese BMI were independent risk factors for systemic inflammation in the ECLIPSE study, whereas self-reported cardiovascular disease was not. Also, in the present study, systemic inflammatory markers were not independent from traditional cardiovascular risk factors associated with arterial stiffness.

Arterial stiffness and PR

Endurance-trained athletes have higher large-artery compliance than do their sedentary counterparts [30], and training improves arterial stiffness in healthy young [31] and elderly subjects [32, 33]. However, the effects of exercise training on arterial stiffness in elderly patient populations are contradictory [34–38]. This issue is further complicated by the heterogeneity among studies in modality, frequency and duration of exercise training, and in the assessment method for arterial stiffness.

VIVODTZEV *et al.* [12] were the first to show significant improvements in brachial pulse wave velocity in 10 patients with COPD who underwent a 4-week aerobic endurance training programme. Peripheral (brachial) muscular arteries are more susceptible to modification by exercise training than central (aortic) elastic arteries [39]. Indeed aortic stiffening is more attributable to elastin degradation and is largely irreversible [40]. Moreover, APWV is the gold standard for measurement of arterial stiffness as it predicts cardiovascular events and mortality in different populations. GALE *et al.* [13] showed a small, but significant, reduction in APWV in an observational study of 32 patients with COPD following an outpatient-based thrice-weekly PR programme including endurance training and resistance training. However, the change in APWV following PR was highly variable. We confirmed the variability of the change in APWV after PR but we were not able to confirm a significant reduction in APWV; even though the number of subjects, the number of PR sessions and baseline APWV were higher in the present study and subjects generally improved on classical rehabilitation outcomes.

There are several possible explanations for this lack of response. Mechanisms underlying arterial stiffness with age, such as elastin degradation, are likely to be enhanced and accelerated in patients with COPD and are unlikely to be influenced by a PR programme of limited duration.

Furthermore, the possible effects of exercise training on arterial stiffness might be influenced by a patient's concurrent pharmacological treatment. Cardiovascular medication [41] and combination therapy of inhaled corticosteroids and long-acting β-agonists (inhaled corticosteroids or long-acting β-agonists) [42] may decrease arterial stiffness and the majority of subjects use these medications chronically. However, nonsignificant changes in APWV were observed in patients who were not known to have cardiovascular disease or were untreated with cardiovascular medication. Earlier studies suggested that sex [43], smoking status, body composition and systemic hypertension could play a role in the effect of exercise on arterial stiffness, but none were found to significantly influence changes in arterial stiffness following PR.

The exercise modalities may explain the lack of decrease in arterial stiffness. In marked contrast to the beneficial effect of aerobic training in healthy younger individuals, it was shown that resistance training increases arterial stiffness in young healthy males [44, 45]. Similar opposite effects of endurance and resistance training on arterial stiffness were seen in a study in hypertensive patients [46]. In patients with type 2 diabetes, an increased APWV was seen after 2 years of endurance and resistance training [39].

Thus, resistance training may have outweighed the effects of endurance training on arterial stiffness. The increase in pulse pressure, which has been considered to be a key feature of arterial stiffening, may be an outcome related to resistance training. Importantly, short-term progressive resistance exercise can lead to appreciable increases in muscle strength for people with COPD, which may carry over to the performance of some daily activities [47]. Indeed, the combination of constant-load/interval and strength training is

recommended in state-of-the-art PR to treat peripheral muscle dysfunction in chronic respiratory disease, because it results in combined improvements in exercise capacity and muscle strength. Nevertheless, it would be interesting to compare the effect of endurance *versus* resistance training on APWV in patients with COPD.

Baseline arterial stiffness correlated very well with the change in arterial stiffness after PR, even after adjustment for possible confounders, such as age, blood pressure, sex and BMI. It is unclear whether and to what extent this correlation could be explained by statistical bias (regression to the mean). Still, the finding is interesting and worth discussing, as the correlation was highly significant. Moreover, in a study evaluating the effect of fluticasone propionate/salmeterol on arterial stiffness in patients with COPD, a decrease in APWV was only seen in patients with a baseline APWV belonging to the highest baseline tertile of the study sample [42]. However, it is noticeable that patients at both extremes (decreasers with high baseline stiffness *versus* increasers with low baseline stiffness) did not differ in terms of disease severity, health status, age, BMI or systemic inflammation. This confirms that arterial stiffness and its change cannot be predicted by these clinical outcomes. It is of note that we did not identify other studies that evaluated differences in characteristics of responders and nonresponders in terms of arterial stiffness and exercise programmes.

A limitation of this study is the lack of a nonexercising COPD control group. Although, it seems reasonable to speculate that APWV does not change during 8 weeks of usual care, a nonexercising COPD control group would have been desirable. A second limitation is the absence of a direct reproducibility analysis at the baseline of the study. Nevertheless, we are confident in the quality and reproducibility of the data in our study, given the strict quality control criteria (see Methods section). Moreover, two recent studies specifically addressed reproducibility of APWV measurements in COPD and found that this was highly reproducible and not affected by lung hyperinflation [48, 49].

A third limitation is that HRCT would have been preferable to evaluate emphysema against arterial stiffness. Finally, heterogeneity among the included COPD patients may have blunted any effects of PR on arterial stiffness. However, phenotyping of patients was extensive and the large number of patients in this study allowed for post-stratification.

In conclusion, central arterial stiffness is increased in subjects with COPD and determined by blood pressure and age. Systemic inflammation does not explain the variance in APWV. Furthermore, although subjects improved on classic rehabilitation outcomes, arterial stiffness is resistant to modification through a state-of-the-art PR programme in patients with COPD in general and in different subgroups. Nevertheless, baseline arterial stiffness did strongly predict the change in stiffness after PR in individual patients. Ultimately, this is a negative study that conflicts with the conventional knowledge that arterial stiffness may be attributed to systemic inflammation and may be a modifiable disease-specific cardiovascular risk factor in COPD. At the same time, this is the largest study performed in COPD in this field.

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