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

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Statement: Arterial stiffness in COPD is not related to systemic inflammation and does not respond to state-of-the-art PR.

**ABSTRACT**

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

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

*Methods:* Aortic pulse wave velocity (APWV) was determined in 168 healthy volunteers and APWV and inflammatory markers in 162 COPD patients during baseline evaluation of a PR-program. A complete post-PR dataset was collected in 129 patients.

*Results:* APWV was increased in COPD patients compared to controls. Blood pressure and age predicted baseline APWV. Systemic inflammatory markers were not independently related to APWV. Although baseline APWV was predictive for the change in APWV after PR (r=-0.77), on average APWV did not change (10.7±2.7 *vs*. 10.9±2.5 m/s; p=0.339).

*Conclusions:* Arterial stiffness in COPD is not related to systemic inflammation and does not respond to state-of-the-art PR. These results emphasize the complexity of cardiovascular risk and its management in COPD.

**ABSTRACT WORD COUNT:** 181

**KEYWORDS:** COPD, arterial stiffness, aortic pulse wave velocity, APWV, pulmonary rehabilitation, systemic inflammation

## 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 the gold standard to measure 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 study in COPD showed weak correlations with IL-6 and soluble tumor necrosis factor receptor 1 (sTNFR1), but not with soluble tumor necrosis factor receptor 2 (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 program on APWV and other functional vascular outcomes.

**METHODS** (See online methods for details)

**Study design and subjects**

The CIRO comorbidity (CIROCO) study (MEC 10-3-067) was a 2-year prospective single-centre study. Patients with COPD were recruited at the start of PR at CIRO+. Study design, in- and exclusion criteria and details of the assessments have been published.[14] Briefly, in addition to comprehensive pre- and post-PR clinical assessment, patients' hemodynamics were 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 seconds of recorded and analyzed 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 seconds measurement. Only when a measurement met the predefined quality thresholds, it was retained. After marking the exact location measurements were repeated three times for securing reproducibility. A measurement was accepted when it was three times reproducible 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 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 smoking healthy elderly without airflow limitation underwent lung function tests and hemodynamic assessments as part of the AGING study. (MEC 10-3-033)

**Pulmonary rehabilitation program:**

CIRO+ provides a state-of-the-art interdisciplinary PR program for patients with COPD consisting of 40 sessions, in line with the latest ATS/ERS Statement on Pulmonary Rehabilitation.[15] During the baseline assessment a careful characterization of the extra-pulmonary features and co-morbidities of patients with COPD was performed, which determined the application of various treatments: physical exercise training, occupational therapy, dietary counseling, psychosocial counseling, education and exacerbation management. Physical exercise training was the cornerstone of the program, consisting of strengthening exercises of muscle groups of 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 dyspnea and fatigue symptom scores. All patients underwent flexibility exercises, general physical exercise for lower and upper extremities, and daily supervised 30-min outdoor walks.

**Statistics**

Statistics were performed using SPSS version 19.0. Results are expressed as mean ± standard deviation or count (percentage). For comparison, Chi square tests, independent samples Student's *t*-test, paired Student's *t*-test, or ANOVA were used where applicable. Relationships between continuous variables were analysed using simple and/or multivariate

linear regression. Figure 2 and 3 were obtained using SAS 9.1. More precisely, a model was constructed for change in APWV including the covariates gender, age, BMI, mean blood pressure and APWV at baseline. Fixed effects only were used since baseline APWV was included as a covariate and only 2 time points were observed. Men at age 60 with BMI at 25 $kg/m^2$, mean blood pressure at 100 mm Hg and a baseline APWV level of 10 m/s 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 (e-Figure 1). Fifty-one of the 213 eligible COPD patients (23.9%) were excluded because of unsuccessful APWV measurement at baseline. Patients with unsuccessful APWV measurements had a significantly higher body mass index (BMI), fat free mass index (FFMI), triglycerides, glucose, diffusion capacity ($D_LCO$) and estimated glomerular filtration rate compared to those with successful measurement (e-Table 1). A total of 162 subjects with successful baseline assessment started PR. Of these, 9 subjects (5.6%) dropped out from the study before the end of the PR program (e-Figure 1). In 24 subjects (15.7%), APWV measurement 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 (e-Tables 2 and 3). Moreover, about 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 subjects are slightly younger and had a slightly higher BMI and higher FFMI, compared to the patients with COPD. As by definition pulmonary function is normal in these subjects. These subjects used less antihypertensive mediction, anxiolytics, antidepressives, calcium suppletion, bisfosfonates or antacids compared to COPD patients. (e-Table 3)

**Hemodynamic measurement in COPD patients and healthy controls.**

Patients with COPD had a significantly higher APWV compared to never smoking, and ex-smoking controls. (Table 2) Consistently, central augmentation index (normalized for a heart rate of 75 beats per minute) was higher in subjects with COPD compared to both control

groups. Ex-smoking controls had a higher peripheral and central blood pressure compared to 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 to both control groups. (Table 2)

**Determinants of APWV in COPD**

APWV did not correlate with systemic levels of leucocytes, C-reactive protein (CRP), interleukin 6 (IL-6), interleukin 8 (IL-8) or sTNFRII. A weak but statistically significant correlation was found between APWV and sTNFRI. After adjusting for age, mean blood pressure, gender 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 the first second ($FEV_1$) % 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. (e-Table 4)

**Effects of pulmonary rehabilitation**

Six-minute walking distance (478 ± 108 to 509 ± 102 meter), cycle endurance (371 ± 275 to 569 ± 396 seconds) , muscle strength (leg press: 103 ± 48 to 128 ± 50 kg), health status (SGRQ: 52.0 ± 19.9 to 48.2 ± 18.7 points), and dyspnea grade (MMRC: 2.14 ± 1.2 to 1.54 ± 1.0

points) improved significantly compared to baseline. (e-table 5) 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 leucocytes did not change following PR. (e-Table 6)

APWV (Figure 1), central or peripheral blood pressure or augmentation index did not change following PR, while peripheral and central pulse pressure increased. A statistically significant, but most probably clinically irrelevant reduction in heart rate was seen. (Table 3) Also after stratification of the study sample in different relevant subgroups, no changes in APWV were noticed after PR. (Table 4)

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, gender and BMI in a linear fixed effects model. (Figure 2) Interestingly, subjects with a low baseline APWV (< 8 m/s (25$^{th}$ percentile of the study sample)) whose APWV values increased by at least 0.5 m/s after PR (n=19) and patients with a high baseline APWV (12.5 m/s (75$^{th}$ percentile of the study sample)) whose APWV values decreased at least 0.5 m/s (n=15) were not different with respect to baseline clinical characteristics, systemic inflammation or PR outcome.

**DISCUSSION**

The main findings of this study are: First, central arterial stiffness is increased in a large sample of subjects with COPD compared to healthy controls, and variance in arterial stiffness

is partially determined by age and resting blood pressure. Second, markers of systemic inflammation do not explain the variance in arterial stiffness in COPD. Third, 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 to healthy control subjects.[7, 17] The current study corroborates these findings. Surprisingly, peripheral (but not central) 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 remodeling 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 remodeling has been suggested in patients with an emphysematous phenotype of COPD.[20] Indeed, McAllister et al. showed a positive correlation between arterial stiffness and HRCT-quantified emphysema in 77 COPD patients.[21] HRCT was not available in our study, but DLCO (as another surrogate for pulmonary emphysema) was not associated with APWV. Although DLCO and CT 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. showed the highest arterial stiffness in nine emphysematous patients with osteoporosis at the hip, compared to 62 emphysematous subjects without osteoporosis. [7] However, these differences were not found for the 13 subjects with osteoporosis at 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, TNF-α, IL-6 and IL-8) have been reported in COPD [25] and several of these have been associated with subclinical atherosclerosis[26] and ischemic 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. IL-6 was also reported to be significantly associated with APWV in multivariate regression, although this needs to be interpreted with caution as also the control subjects were included in the regression analysis.[7] In our study, the multivariate model only included patients with COPD.

Systemic inflammation is thought to accelerate and stimulate the vascular extracellular matrix remodeling process of elastin fragmentation and collagen deposition, resulting in arterial stiffness.[19] However, evidence for a causal relationship between low-grade systemic inflammation and 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 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 one 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 pulmonary rehabilitation**

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. were the first to show significant improvements in brachial pulse wave velocity in 7 patients with COPD who underwent a 4 week aerobic endurance training

program .[12] 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 pulmonary rehabilitation program 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 like elastin degradation are likely to be enhanced and accelerated in patients with COPD and are unlikely to be influenced by a PR program of limited duration. Furthermore, the possible effects of exercise training on arterial stiffness might be influenced by patients concurrent pharmacological treatment. Cardiovascular medication[41] and combination therapy of inhaled corticosteroids and long-acting β-agonists (ICS/LABA)[42] may decrease arterial stiffness and the majority of subjects use these medications chronically. However, non-significant changes in APWV were observed in patients who were unknown with cardiovascular disease or untreated with cardiovascular medication. Earlier studies suggested that gender[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 for the lack of decrease in arterial stiffness. In marked contrast to beneficial effect of aerobic training in healthy younger individuals, it was shown that resistance training increases arterial stiffness in young healthy men.[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 two years of endurance and resistance training.[39]

So, resistance training may have outweighed the effects of endurance training on arterial stiffness. The increase in pulse pressure, which has been considered 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 pulmonary rehabilitation 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 like age, blood pressure, gender and BMI. It is not sure whether and to what extent this correlation could be explained by statistical bias known as 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. Of notice, we did not identify other studies that evaluated differences in characteristics of responders and non-responders in terms of arterial stiffness and exercise programs.

A limitation of this study is the lack of a non-exercising COPD control group. Although, it seems reasonable to speculate that APWV does not change during eight weeks of usual care, a non-exercising COPD control group would have been desirable. A second limitation is the absence of a direct reproducibility analysis at baseline of the study. Nevertheless we are confident with the quality and reproducibility of the data in this study, given the strict quality control criteria (see methods). 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 high resolution computer tomography 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 state-of-the-art PR program 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 which conflicts with the conventional wisdom 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 yet performed in COPD in this field.

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**Table 1: Baseline characteristics of 162 COPD patients with APWV.**

| | **COPD n=162** | **Never smoking controls n=65** | **Ex-smoking controls n=102** |
|---|---|---|---|
| *Demographics* | | | |
| Age, years | 63.8 ± 6.9 | 57.9 ± 8.1* | 61.4 ± 6.7*# |
| Male, n (%) | 97 (59.9%) | 31 (47.0%)* | 47 (45.6%)* |
| Active smoker, n (%) | 47 (29.0) | 0 | 0 |
| Long-term oxygen therapy, n (%) | 22 (13.6) | 0 | 0 |
| 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* | | | |
| $FEV_1$, liter | 1.40 ± 0.55 | 3.4 ± 0.9* | 3.3 ± 0.9* |
| $FEV_1$, % predicted | 51.4 ± 17.4 | 119.6 ± 14.8* | 119.2 ± 17.7* |
| $FEV_1$/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* | | | |
| $PaCO_2$, kPa | 5.3 ± 0.6 | | |
| $PaO_2$, kPa | 9.5 ± 1.1 | | |
| $O_2$ saturation, % | 94.4 ± 7.6 | | |
| *Functional outcome* | | | |
| 6-MWD, meter | 475 ± 108 | | |
| CWRT time, seconds | 359 ± 284 | | |
| Leg press, kg | 101 ± 47 | | |
| mMRC, grade | 2.1 ± 1.1 | | |
| SGRQ, points | 51.6 ± 18.4 | | |
| *Charlson comorbidy index* | 1.57 ± 0.89 | | |
| Myocardial infarction, n (%) | 16 (9.9) | | |
| Heart failure, n (%) | 5 (3.1) | | |
| Peripheral arterial disease, n (%) | 30 (18.5) | | |
| Cerebrovascular disease, n (%) | 14 (8.6) | | |
| Any cardiovascular disease, n (%) | 50 (30.9) | | |
| Diabetes, n (%) | 7 (4.3) | | |
| *Clinical chemistry* | | | |
| Triglycerides, mmol/L | 1.5 ± 0.7 | | |
| LDL, mmol/L | 2.9 ± 1.0 | | |
| HDL, mmol/L | 1.7 ± 0.5 | | |
| Glucose (mmol/L) | 5.7 ± 0.7 | | |

| | | |
|---|---|---|
| Creatinin | 87.5 ± 22.6 | |
| eGFR, ml/min | 75.9 ± 21.5 | |
| *Systemic inflammatory markers* | | |
| CRP, mg/l | 4,6 ± 6,1 | |
| IL-6, pgs/ml | 3.3 ± 4.5 | |
| IL-8, pgs/ml | 13.0 ± 5.3 | |
| sTNFRI, pgs/ml | 2186 ± 771 | |
| sTNFRII, pgs/ml | 3714 ± 1435 | |
| Leucocytes $*10^9$/L | 7.5 ± 2.0 | |

Legend: Summary variables are presented as mean ± standard deviation for quantitative variables, and count (percentage) for discrete variables. FEV1: Forced expiratory volume in the first second; $D_LCO$: Diffusion factor for carbon monoxide; mMRC: Modified Medical Research Council; 6MWD: Six minute walking distance; CWRT: continuous work rate test; SGRQ: St.-George's Respiratory Questionnaire, BODE index: Based on BMI, Obstruction (FEV1), Dyspnea, Exercise (6MWD); LDL: low density lipoprotein; HDL: high density lipoprotein; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; IL-6: interleukin 6; IL-8: interleukin 8; sTNFRI: Soluble tumor necrosis factor-α receptor I; sTNFRII: Soluble tumor necrosis factor-α receptor II. * significantly ($p<0.05$) different in comparison with subjects with COPD. # significantly ($p<0.05$) different in comparison with never-smoking controls.

| *Hemodynamic measurements* | **COPD (n=162)** | **Never smoking controls (n=65)** | **Ex-smoking controls (n=102)** |
|---|---|---|---|
| Aortic pulse wave velocity, m/s | 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 systolic pressure, mm Hg | 137 ± 21 | 141 ± 17 | 146 ± 21* |
| Peripheral diastolic pressure, mm Hg | 82 ± 10 | 84 ± 8 | 85 ± 9* |
| Peripheral mean pressure, mm Hg | 102 ± 13 | 105 ± 11 | 108 ± 13* |
| Peripheral pulse pressure, mm Hg | 55 ± 16 | 57 ± 13 | 61 ± 16* |
| Heart Rate, beats per minute | 68 ± 11 | 58 ± 8* | 59 ± 8* |
| Central systolic pressure, mm Hg | 129 ± 20 | 133 ± 16 | 138 ± 21* |
| Central diastolic pressure, mm Hg | 83 ± 10 | 85 ± 9 | 86 ± 9* |
| Central mean pressure, mm Hg | 102 ± 13 | 105 ± 11 | 108 ± 13* |
| Central pulse pressure, mm Hg | 45.9 ± 15.0 | 45.5 ± 13 | 44.5 ± 11* |

Legend: * significantly ($p<0.05$) different in comparison with subjects with COPD. # significantly ($p<0.05$) different in comparison with never-smoking controls.

**Table 2: Simple and multivariate linear regression with APWV as the dependent variable.**

| | Simple linear regression | | | Multivariate linear regression* | | | |
|---|---|---|---|---|---|---|---|
| | **Beta** | **t-test** | **p-value** | **Beta** | **t-test** | **p-value** | **F change of the model#** |
| CRP, ngs/ml | 0.134 | 1.584 | 0.116 | 0.098 | 1.325 | 0.187 | -6.044 |
| IL-6, pgs/ml | 0.065 | 0.761 | 0.448 | 0.017 | 0.231 | 0.818 | -6.477 |
| IL-8, pgs/ml | 0.101 | 1.192 | 0.235 | 0.101 | 1.357 | 0.177 | -6.165 |
| sTNFRI, pgs/ml | 0.171 | 2.034 | 0.044 | 0.064 | 0.791 | 0.430 | -6.373 |
| sTNFRII, pgs/ml | 0.126 | 1.488 | 0.139 | -0.013 | -0.165 | 0.869 | -6.472 |
| Leucocytes $*10^9$/L | 0.043 | 0.547 | 0.585 | 0.022 | 0.327 | 0.744 | -3.185 |

Legend: *adjusting for age, mean blood pressure, gender and BMI. CRP: C-reactive protein, sTNFRI: Soluble tumor necrosis factor-α receptor I, sTNFRII: Soluble tumor necrosis factor-α receptor II, IL-6: interleukin 6; IL-8: interleukin 8. #: F of the model with age, mean blood pressure, gender and BMI = 15.66

**Table 3: Differences in APWV and other hemodynamics in subjects who completed PR.**

| N=129 | **baseline** | **after PR** | **p** |
|---|---|---|---|
| Aortic pulse wave velocity, m/s | 10.7 ± 2.7 | 10.9 ± 2.5 | 0.339 |
| Central augmentation index, % | 30.8 ± 8.1 | 30.2 ± 8.1 | 0.129 |
| Peripheral systolic pressure, mm Hg | 135 ± 19 | 137 ± 19 | 0.064 |
| Peripheral diastolic pressure, mm Hg | 81 ± 9 | 81 ± 9 | 0.377 |
| Peripheral mean pressure, mm Hg | 101 ± 12 | 101 ± 12 | 0.427 |
| Peripheral pulse pressure, mm Hg | 54 ± 15 | 57 ± 15 | 0.004 |
| Heart Rate, beats per minute | 68 ± 11 | 67 ± 11 | 0.032 |
| Central sytolic pressure, mm Hg | 127 ± 18 | 129 ± 19 | 0.061 |
| Central diastolic pressure, mm Hg | 82 ± 9 | 82 ± 9 | 0.386 |
| Central mean pressure, mm Hg | 101 ± 12 | 101 ± 12 | 0.428 |
| Central pulse pressure, mm Hg | 44 ± 14 | 47 ± 14 | 0.003 |

Legend: Variables are presented as mean ± standard deviation.

**Table 4: Difference in APWV after PR in different subgroups**

| | n | APWV baseline | APWV after PR | p |
|---|---|---|---|---|
| Overweight and obese | n=65 | 10.9±2.7 | 11.2±2.3 | 0.315 |
| Underweight | n=23 | 10.3±2.8 | 10.4±3.2 | 0.830 |
| No blood pressure lowering medication | n=79 | 10.5±2.6 | 10.7±2.4 | 0.383 |
| No lipid lowering drugs | n=92 | 10.5±2.7 | 10.7±2.4 | 0.209 |
| No cardiovascular medical history according to the CCI | n=60 | 10.3±2.6 | 10.6±2.5 | 0.232 |
| No blood pressure lowering medication and no lipid lowering drugs | n=69 | 10.4±2.7 | 10.7±2.5 | 0.340 |
| No cardiovascular medical history according to the CCI | n=60 | 10.3±2.6 | 10.6±2.5 | 0.232 |
| No blood pressure lowering medication and no lipid lowering drugs and no cardiovascular medical history according to CCI | n=60 | 10.3±2.6 | 10.6±2.5 | 0.244 |
| Active smokers | n=35 | 10.5±2.9 | 10.3±2.5 | 0.593 |
| Ex-smokers | n=94 | 10.8±2.7 | 11.1±2.5 | 0.151 |
| Men | n=80 | 11.2±2.8 | 11.5±2.7 | 0.520 |
| Women | n=49 | 9.8±2.4 | 10.0±1.8 | 0.417 |
| Improvement of >50 m in 6MWD and more than 4 points on SGRQ | n=25 | 10.4±2.7 | 10.4±1.9 | 0.954 |
| Normal blood pressure (<140/90 mm Hg) | n=79 | 10.0±2.5 | 10.2±2.4 | 0.395 |
| Hypertensives (>140/90 mm Hg) | n=49 | 11.8±2.7 | 12.0±2.3 | 0.585 |

Legend: Variables are presented as mean ± standard deviation. CCI: Charlson comorbidity index.

**Figure legends:**

**Figure 1: Data plot for APWV in each patient before and after pulmonary rehabilitation.**

Legend: The thick circles and connecting line illustrate the mean.

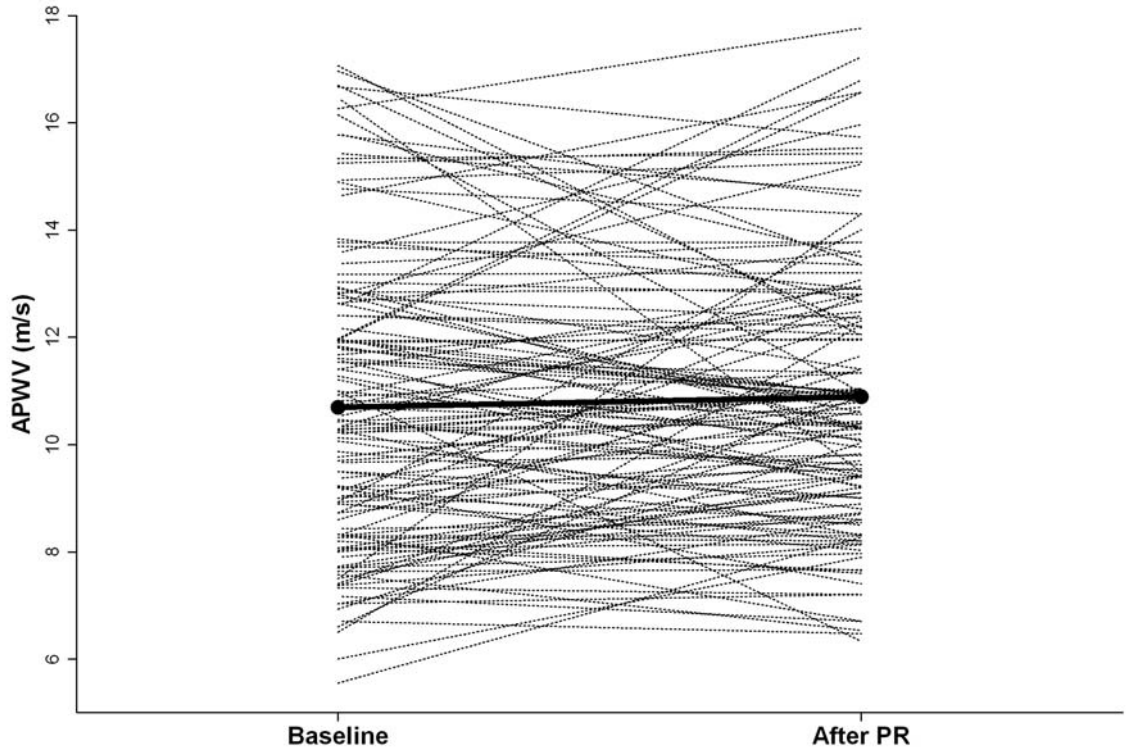

**Figure 2: Covariate adjusted change in APWV after PR in function of baseline APWV level.**

Change in APWV is adjusted for age, mean blood pressure, gender and BMI. The histogram (Figure A) shows the distribution of the change in APWV after PR. Figure B shows the change in APWV after PR in function of the baseline APWV level for men (black circles) and women (red circles). (Correlation: r= -0.77, p<0.001)