Thorax Online First, published on November 16, 2007 as 10.1136/thx.2007.083493

ORIGINAL ARTICLE

Increased arterial stiffness in patients with chronic obstructive pulmonary disease; *a mechanism for increased cardiovascular risk*

COPD and arterial stiffness

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Support: National Institute of Health (RFA-HL-02-005)
Chief Scientists Office Programme Support Grant
British Cardiovascular Society Research Fellowship

Word count: 2,877 **Figures and tables:** 7
Abstract: 228 **References:** 35

Key words: COPD ■ arterial stiffness ■ blood pressure ■ inflammation ■ CRP

Manuscript ID: THORAX/2007/083493

ABSTRACT

Rationale

Chronic obstructive pulmonary disease (COPD) is associated with a 2-3 fold increase in the risk of ischemic heart disease, stroke and sudden death. The mechanisms responsible for this association are not clear and appear to be independent of smoking history.

Objective

We test the hypothesis that patients with COPD have increased arterial stiffness and blood pressure in comparison to age and smoking matched controls.

Methods and Main Results

In a prospective case-control study, we recruited 102 patients with COPD and 103 age- and smoking status-matched healthy controls. Patients were assessed by clinical history and spirometry with arterial stiffness and blood pressure determined using radial artery applanation tonometry and sphygmomanometry.

Patients with COPD had increased arterial stiffness when compared to matched controls, with elevated augmentation pressure (17(1) vs. 14(1) mmHg; p=0.005), and a reduced time to wave reflection (131(1) vs. 137(2) ms; p=0.004). These differences were associated with increases in both diastolic (82(1) vs. 78(1) mmHg; p=0.005) and systolic blood pressure (147(2) vs. 132(2) mmHg; p<0.001). High-sensitive serum C-reactive protein concentrations were 3-fold higher in patients (6.1(0.9) vs. 2.3(0.4) mg/L; p=0.001). Data are presented as mean (SEM).

Conclusions

Patients with COPD have increased arterial stiffness and blood pressure in comparison with age- and smoking-status matched controls. We speculate that increased systemic inflammation and vascular dysfunction could potentially explain the excess cardiovascular morbidity and mortality associated with COPD.

INTRODUCTION

Although primarily a lung disease, chronic obstructive airways disease (COPD) is now recognised to have important systemic consequences that may affect morbidity and mortality.[1] In particular, it is associated with a markedly increased risk of cardiovascular disease.[2] Observational studies suggest that reduced expiratory flow volume (FEV_1), a characteristic feature of COPD, is associated with a ~3-fold increase in risk of ischemic heart disease, stroke and sudden death with cardiovascular mortality accounting for up to 50% of all deaths in patients with COPD.[3,4] While most patients with COPD are current or ex-smokers, this increased cardiovascular risk is independent of cigarette smoking habit.[2,5]

The mechanisms of increased cardiovascular risk in COPD remain poorly understood. COPD is characterised by excessive pulmonary inflammation in response to cigarette smoking and air pollution.[6] However it is increasingly recognised that COPD is also associated with a systemic inflammatory response.[7] During the last 10 years the role of inflammation and oxidative stress in the pathogenesis of atherosclerosis has been established.[8] The inflammatory mediator C-reactive protein (CRP) is an important predictor of cardiovascular outcome in patients with and without coronary artery disease, and has been directly implicated in the pathogenesis of atherosclerotic plaque formation. CRP is increased along with a variety of acute phase proteins in patients with COPD,[9] and may contribute to the development and clinical complications of atherosclerosis in these patients.

Atherosclerosis is a disease of the large and medium sized elastic arteries in which one of the earliest pathological features is endothelial dysfunction.[10] The vascular endothelium plays an important role in the maintenance of vascular tone through the local release of vasoactive compounds such as nitric oxide. With increasing age and in the presence of cardiovascular risk factors, vascular dysfunction contributes to reduced arterial compliance and increased central arterial pressure.[11] Increased large artery stiffness results in greater central aortic systolic pressures, increased left ventricular after-load and reduced diastolic coronary artery filling. Arterial stiffness may be the central pathological process involved in essential hypertension and is an independent predictor of cardiovascular mortality in these patients.[12]

Applanation tonometry of the radial artery and pulse wave analysis can be used to derive measures of arterial stiffness and central aortic blood pressure. Previously, central arterial stiffness has been linked to reduced FEV_1 in apparently healthy men without coronary heart disease.[13] Increased central arterial stiffness and blood pressure in patients with COPD may explain the excess cardiovascular morbidity and mortality in these patients. In a prospective case-control study, we assessed arterial stiffness and blood pressure in patients with COPD and controls matched for age and current smoking status.

METHODS

Subjects

Patients with COPD were recruited through general practice databases and a specialised outpatient clinic at the Royal Infirmary of Edinburgh. COPD was defined by European Respiratory Society /American Thoracic Society guidelines.[14] Patients with a recent exacerbation (within 6 weeks), were excluded. COPD patients with a history of asthma, bronchiectasis, pulmonary fibrosis, pneumonectomy or pulmonary lobectomy, rheumatoid arthritis, inflammatory bowel disease, connective tissue disorders, or malignancy within the previous 5 years and those treated with long term steroids, oral theophylline or immunosuppressive therapy were excluded. Healthy controls recruited through primary care and were not taking any regular medication. Cases and controls were matched by frequency for age and current smoking status using the mean values for each group. All studies were performed with local ethical approval, written informed consent of all subjects and in accordance with the Declaration of Helsinki.

Study design

In a prospective case-control study, we recruited 102 patients with COPD, and 103 healthy controls matched for age and current smoking status. Subjects were asked to refrain from smoking for 12 hours prior to assessment. Prior to assessment all medications were withheld for at least 12 hours, with long acting anti-cholinergic treatment withheld for 24 hours. A sub-group of COPD patients with no history of cardiovascular comorbidities was identified. From the history and medical records this group had no prior diagnosis of, and were not on medication for, ischaemic heart disease, hypertension, hypercholesterolaemia or diabetes mellitus. Using the same criteria, control subjects were screened for these cardiovascular risk factors prior to inclusion.

Pulse wave analysis

Vascular studies were performed in a quiet, temperature controlled room with subjects resting in a supine position. Systolic and diastolic blood pressures were measured in duplicate using a semi-automated non-invasive oscillometric sphygmomanometer, following a 10 min rest period. Pulse wave analysis was performed using micromanometer (Millar Instruments, Texas) applanation tonometry of the radial artery at the wrist and the SphygmoCor™ system (AtCor Medical, Sydney), in accordance with the manufacturer's recommendations. Briefly, pulse wave analysis derives an aortic pulse pressure waveform from the radial artery wave via a mathematical transfer function. The arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave generated by peripheral vascular resistance (Figure 1).[15] The augmentation index, which is the difference between the second and first systolic peaks expressed as a percentage of the pulse pressure, is a measure of systemic arterial stiffness and wave reflection. The time to wave reflection (Tr) is reduced with increasing arterial stiffness, and provides a surrogate of aortic pulse wave velocity.[16]

At least two independent waveform analyses were obtained from each subject, with measurements only accepted upon meeting SphygmoCor™ quality control criteria. These replicate measures of augmentation pressure were highly correlated across the study population (r=0.939, p<0.0001, n=205). Measurements were performed by staff specifically trained in the technique and blinded to the clinical characteristics of each subject.

Assays

Differential white blood cell count, and platelets were determined using an autoanalyzer. Serum lipid profile was determined by the regional accredited clinical biochemistry laboratory. Serum CRP concentrations were measured using a highly sensitive immunonephelometric assay (Behring BN II nephelometer, Marburg, Germany).

Data analysis and statistics

Data were analysed using SPSS (Version 14). Comparisons were made between COPD patients and matched controls using unpaired t-tests for continuous variables and Chi-squared analysis for categorical data. Comparisons were made between controls and the two pre-specified COPD sub-groups, those patients with or without a history of cardiovascular co-morbidities, using analysis of variance (ANOVA). Correlations between hsCRP and measures of arterial stiffness were analysed in COPD patients and controls using the Pearson's correlation coefficient. Continuous variables were reported as mean (SEM) and statistical significance was taken at $p<0.05$.

RESULTS

The populations were matched for age and current smoking status (Table 1). In COPD patients mean post-bronchodilator FEV1 was 46(2)% predicted, post-bronchodilator FVC 68(2)% predicted, and FEV1/FVC ratio 50 (1)% predicted. When stratified by Global initiative for chronic Obstructive Lung Disease (GOLD) stage, 2% of patients were stage I, 36% stage II, 39% stage III and 20% stage IV. Whilst well matched for current smoking status, there was a modest yet significant difference between patients and controls (46±2 *versus* 33±2 pack years, p=0.004). Weight (p=0.005) and body mass index (p=0.014) were reduced in patients with COPD compared to healthy controls. In patients with COPD, lipid profiles were similar in the presence or absence of established cardiovascular comorbidities. Serum CRP concentrations were higher in the COPD groups than in controls (p=0.001).

Table 1. Baseline characteristics of patients with chronic obstructive pulmonary disease (COPD) and matched healthy controls

	Healthy controls	**COPD patients**	**p value**
	n=103	**n=102**	
Sex, male/female	51/52	61/41	0.161
Age, years	66.7 (0.7)	67.1 (0.7)	0.677
Current smoker	49 (48)	48 (47)	1.000
Ex-smoker	54 (52)	54 (53)	1.000
Serum total cholesterol, mmol/l	5.5 (0.1)	5.7 (0.1)	0.329
LDL cholesterol, mmol/l	3.2 (0.1)	3.1 (0.1)	0.444
HDL cholesterol, mmol/l	1.5 (0.1)	1.6 (0.1)	0.335
C-reactive Protein, mg/l	2.3 (0.4)	6.1 (0.9)	0.001
Height, cm	168 (0.9)	164 (2.3)	0.097
Weight, kg	76 (1.3)	69 (2.2)	0.005
Body Mass Index, kg/m^2	27 (0.4)	25 (0.7)	0.014

Values presented as mean (SEM) or number (%)
Significance (p): unpaired t-test (continuous variables), chi-squared (categorical data)
IHD = ischaemic heart disease, LDL = low density lipoprotein, HDL = high density lipoprotein

Table 2. Baseline characteristics of patients with chronic obstructive pulmonary disease (COPD) with and without established cardiovascular co-morbidities

	COPD with CV co-morbidity	**COPD without CV co-morbidity**	**p value**
	n = 47	**n = 55**	
Sex, male/female	28/19	33/22	1.00
Age, years	67.3 (1.0)	66.9 (1.0)	0.217
Current smoker	19 (40)	29 (53)	0.238
Ex-smoker	28 (60)	26 (47)	0.238
Serum total cholesterol, mmol/l	5.5 (0.2)	5.8 (0.1)	0.118
LDL cholesterol, mmol/l	2.9 (0.2)	3.2 (0.2)	0.376
HDL cholesterol, mmol/l	1.4 (0.1)	1.7 (0.1)	0.670
C-reactive Protein, mg/l	6.8 (1.7)	5.4 (0.7)	0.115
Height, cm	162 (3.0)	165 (3.4)	0.982
Weight, kg	70 (3.2)	69 (3.0)	0.756
Body Mass Index, kg/m^2	26 (1.1)	24 (0.8)	0.092

Values presented as mean (SEM) or number (%)
Significance (p) unpaired t-test or chi-squared
CV = cardiovascular, LDL = low density lipoprotein, HDL = high density lipoprotein

Table 3. Arterial stiffness and blood pressure in patients with chronic obstructive pulmonary disease (COPD) and matched healthy controls

	Healthy controls n = 103	COPD with CV co-morbidity n = 47	COPD without CV co-morbidity n = 55	p value
Heart rate, bpm	67 (1)	69 (2)	69 (2)	0.621
Peripheral sBP, mmHg	132 (2)	149 (3.5)	146 (3)	0.000
Peripheral dBP, mmHg	78 (1)	82 (2)	83 (2)	0.019
Peripheral MAP, mmHg	96 (1)	105 (2)	104 (2)	0.000
Peripheral PP, mmHg	54 (1)	68 (3)	63 (2)	0.000
Central sBP, mmHg	123 (2)	137 (3)	134 (3)	0.000
Central dBP, mmHg	79 (1)	83 (2)	84 (2)	0.011
Central MAP, mmHg	99 (1)	105 (2)	104 (2)	0.045
Central PP, mmHg	45 (1)	54 (3)	51 (2)	0.001
Augmentation pressure, mmHg	14 (1)	17 (1)	16 (1)	0.016
Augmentation Index, %	30 (1)	31 (2)	31 (1)	0.628
Time to reflection, ms	137 (2)	131 (2)	131 (2)	0.015

Values presented as mean (SEM)
Groups compared with ANOVA
sBP = systolic blood pressure, dBP = diastolic blood pressure, MAP = mean arterial pressure, PP = pulse pressure

The two pre-specified COPD sub-groups, those patients with or without a history of cardiovascular co-morbidities, were well matched (Table 2). Patients with COPD had increased arterial stiffness when compared to matched controls (Table 3), with elevated augmentation pressures (17(1) vs. 14(1) mmHg; p=0.015; Figure 2), and a reduced time to wave reflection (131(1) vs. 137(2) ms; p=0.005; Figure 3). These relationships remained significant in the COPD sub-group with no history cardiovascular comorbidities. Consistent with increased arterial stiffness, these differences were associated with increases in both systolic (147(2) vs. 132(2) mmHg; p<0.001) and diastolic (82(1) vs. 78(1) mmHg; p=0.007) blood pressure. Serum CRP concentrations were 3-fold higher in patients than in controls (6.0(0.9) vs. 2.3(0.4) mg/L; p=0.001; Figure 4). Serum CRP concentrations correlated with augmentation pressure in COPD patients (r=0.736, p=0.034) but not in controls (r=-0.154, p=0.21).

DISCUSSION

Patients with COPD have increased arterial stiffness, blood pressure and systemic inflammation in comparison with controls matched for age and current smoking status. These differences are not due to the presence of co-morbidity in COPD patients as arterial stiffness and pressure measurements were similar in the subgroup of patients without existing ischaemic heart disease, hypertension, hypercholesterolaemia or diabetes mellitus. These findings provide a plausible mechanism for the increased cardiovascular morbidity and mortality associated with COPD.

Arterial stiffness

Increased large artery stiffness in patients with COPD was associated with higher peripheral systolic and diastolic blood pressures. Whilst a number of factors may influence arterial tone and blood pressure in these patients, it is possible that increased large artery stiffness is the major determinant of increased blood pressure and hence cardiovascular risk in patients with COPD. Recently it has been established that measures of arterial stiffness including augmentation and central pulse pressure independently predict adverse clinical outcome in patients with hypertension.[17]

Arterial stiffness is influenced by both structural and functional aspects of the conduit arteries and resistance beds. Atherosclerosis and calcification of the large arteries decreases vascular compliance and structural changes in the vessel wall may explain the increased arterial stiffness observed in patients with COPD. Arterial stiffness and calcification increases with age. The average age of our patients was 67 years and yet augmentation pressures were similar to those of a healthy group of 80 year olds, suggesting that COPD may result in premature ageing of the vasculature.[11] Augmentation pressures in COPD patients were greater than those of a similar aged population with documented coronary artery disease.[18] Consistent with this hypothesis, cigarette smoking and impaired lung function are associated with premature ageing and morphologic abnormalities in the dermis with reduced elastic fibre content.[19] It is possible that excessive neutrophil elastase activity in cigarette smokers and patients with COPD [5,20] results in consumption of elastic fibres in the media of the large arteries leading to arterial stiffness.

Arterial stiffness is also determined by the functional properties of the vessel wall with endothelium-dependent vasomotor tone involved in the dynamic modulation of augmentation pressure.[21-22] There is extensive evidence of endothelial dysfunction in cigarette smokers and in patients with atherosclerosis.[23-24] Whether COPD causes an additional impairment of systemic endothelial dysfunction is not yet known. However, local inflammation is associated with endothelial dysfunction in the pulmonary vasculature [25] and it seems likely that similar processes may influence the extra-pulmonary vasculature. Using *Salmonella typhus* vaccination as a model of acute systemic inflammation, recent work suggests that inflammation can acutely increase aortic stiffness.[26] This model has also been shown to transiently but profoundly alter systemic endothelial function.[27] Interestingly, Kampus *et al* demonstrated that serum

CRP concentrations are positively correlated with indices of arterial stiffness in healthy individuals.[28]

Serum CRP concentrations were elevated in our patients and similar findings have been reported in other published COPD cohorts.[9,29] We hypothesise that systemic inflammation and vascular dysfunction may be responsible for our findings of increased blood pressure and arterial stiffness in COPD. The COPD patients in our cohort had a lower body mass index than healthy controls. This is a recognised feature of COPD and is likely to be due to persistent bronchial and systemic inflammation.[1] Serum CRP concentrations correlated with augmentation pressure in COPD patients, but not in matched controls.

Hypertension

Our findings emphasise the need for better monitoring and treatment of traditional cardiovascular risk factors in patients with COPD. Based on Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines,[30] two-thirds of our COPD population had blood pressures compatible with a diagnosis of hypertension, compared to just one-third of the age-matched controls. These findings are in keeping with a recently published prospective cohort study in which the prevalence of hypertension was approximately 50% in 5,648 COPD patients.[31] Observational studies indicate that death from ischemic heart disease and stroke increases linearly with blood pressure in all age groups.[32] For every 20 mmHg systolic or 10 mmHg diastolic increase in blood pressure, there is a doubling of cardiovascular mortality. A number of factors in addition to increased arterial stiffness may be responsible for the hypertension observed in patients with COPD.

Study limitations

One potential limitation in our study design is that many of the patients with COPD were recruited from a tertiary referral centre. This may have introduced some bias towards increased co-morbidity that could potentially explain the observed differences between patients and controls. In order to counter this potential bias, we undertook a subgroup analysis in which patients with ischemic heart disease and previously recognised cardiovascular risk factors were excluded. Differences in arterial stiffness and blood pressure persisted even when these patients were excluded.

While patients with COPD were characterised carefully with spirometry and reversibility, lung function was not measured in the healthy control group. It is possible that a minority of asymptomatic smokers had undiagnosed airways obstruction, although if anything inclusion of these subjects would be likely to reduce any important differences between the two groups. Whilst we carefully matched patients with controls to ensure an equal balance of current smokers and ex-smokers to avoid the well-established vascular and inflammatory effects of active smoking, there were differences in the number of pack years smoked between the cohorts. It is difficult to control fully for the cumulative effects of cigarette smoke in a case-control study, as an abnormal inflammatory response in the lungs to cigarette smoke is central to the pathogenesis of COPD. Cigarette smoke has a well documented acute effect on blood pressure and arterial stiffness [33] and both are increased in current smokers compared to non-smokers.[34] However a relationship between arterial stiffness or blood pressure and the magnitude of previous cigarette exposure (pack-years) has not been established. We found no association between pack years smoked and any of the vascular parameters measured, and do not believe that small differences in past cigarette exposure account for the reported differences in vascular function between COPD patients and controls.

Conclusions

Patients with COPD have increased arterial stiffness, blood pressure and systemic inflammation. We hypothesise that systemic inflammation and vascular dysfunction may explain the excess cardiovascular morbidity and mortality associated with COPD. Further research into the mechanisms responsible for the increase in arterial stiffness is warranted. Increased awareness and targeted treatment of cardiovascular risk and hypertension has the potential to reduce morbidity and improve prognosis in COPD.

ACKNOWLEDGEMENTS

We would like to thank the Clinical Research Facility, Royal Infirmary Edinburgh, for their assistance with the studies.

COMPETING INTERESTS

None declared

FUNDING

The studies are supported by a National Institute of Health Grant (RFA-HL-02-005) and a Programme Development Grant from the Chief Scientists Office, Scotland. Dr Mills is supported by a Michael Davies Research Fellowship from the British Cardiac Society.

FIGURE LEGEND

Figure 1. An aortic pulse waveform as produced by the SphygmoCor™ system from applanation tonometry of the radial artery. Augmentation pressure is the difference between the systolic peak (forward wave) and first systolic inflection (reflected wave) pressures. This difference divided by the pulse pressure generates the augmentation index. Figure adapted from Smith *et al* 2000.[35]

Figure 2. Mean augmentation pressure, a measure of arterial stiffness, was greater in patients with chronic obstructive pulmonary disease (COPD) (p=0.005) and the subgroup of patients with COPD and no cardiovascular co-morbidity (p=0.04) compared to healthy age- and current smoking status matched controls.

Figure 3. Mean time to wave reflection is reduced in patients with chronic obstructive pulmonary disease (COPD) (p=0.004) and the subgroup of patients with COPD and no cardiovascular co-morbidity (p=0.03) compared to healthy age- and current smoking status matched controls.

Figure 4. Mean serum C-reactive protein (CRP) concentrations (mg/L) are increased in patients with chronic obstructive pulmonary disease (COPD) in the presence or absence of established cardiovascular co-morbidity (p=0.001 for both).

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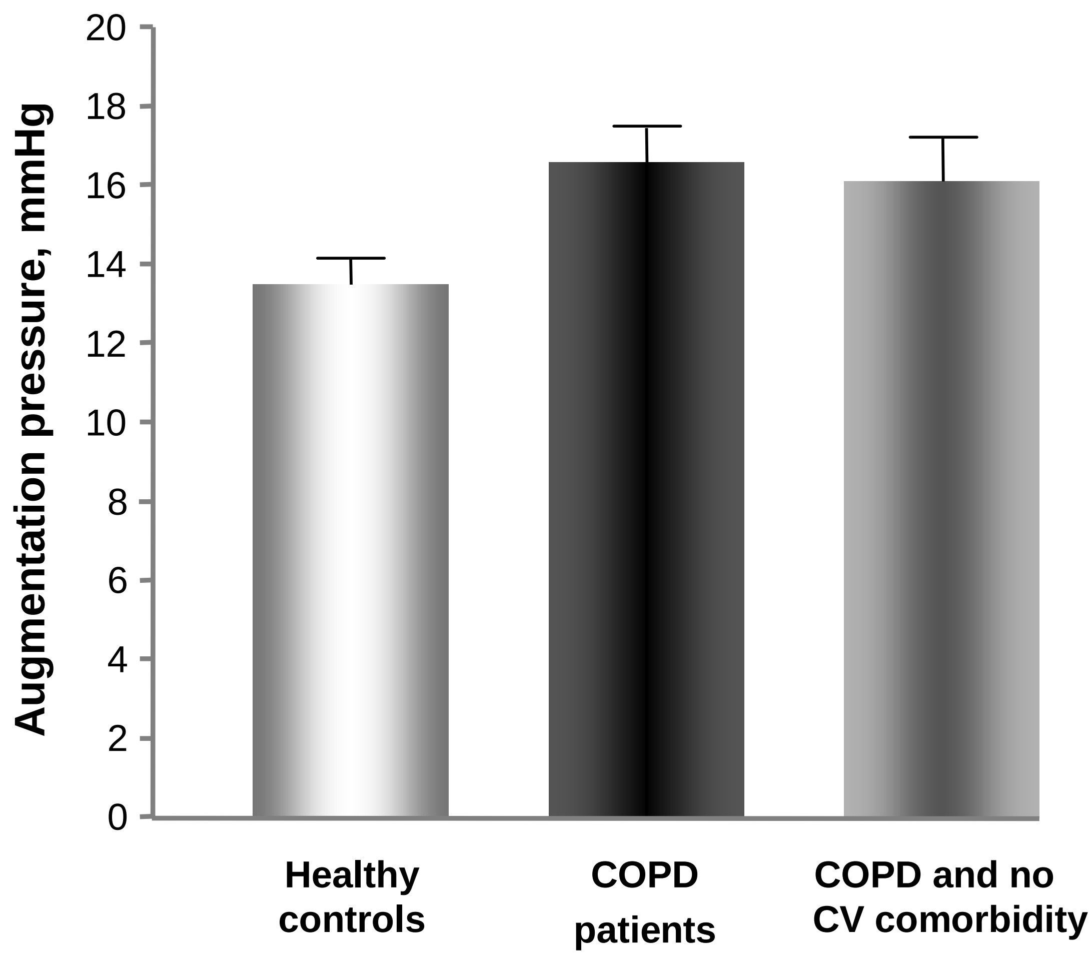
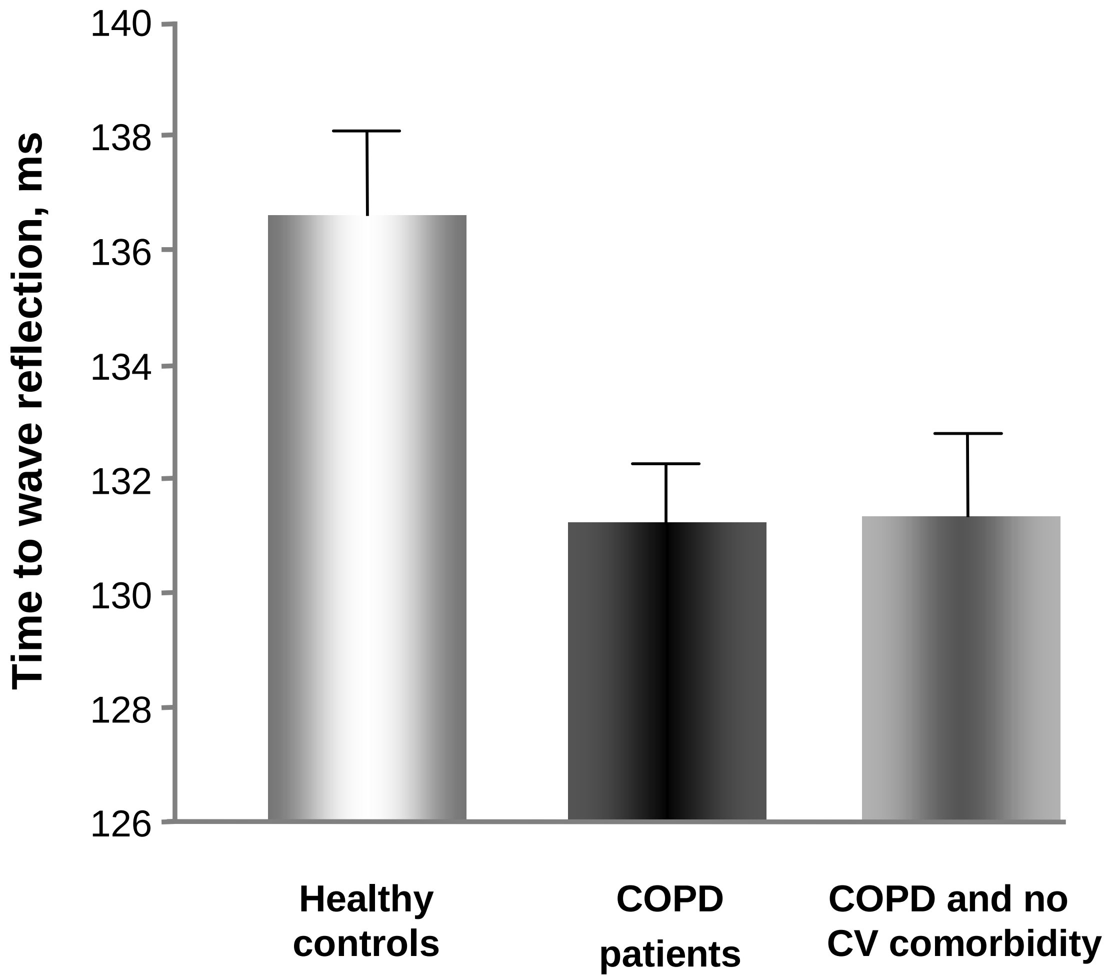
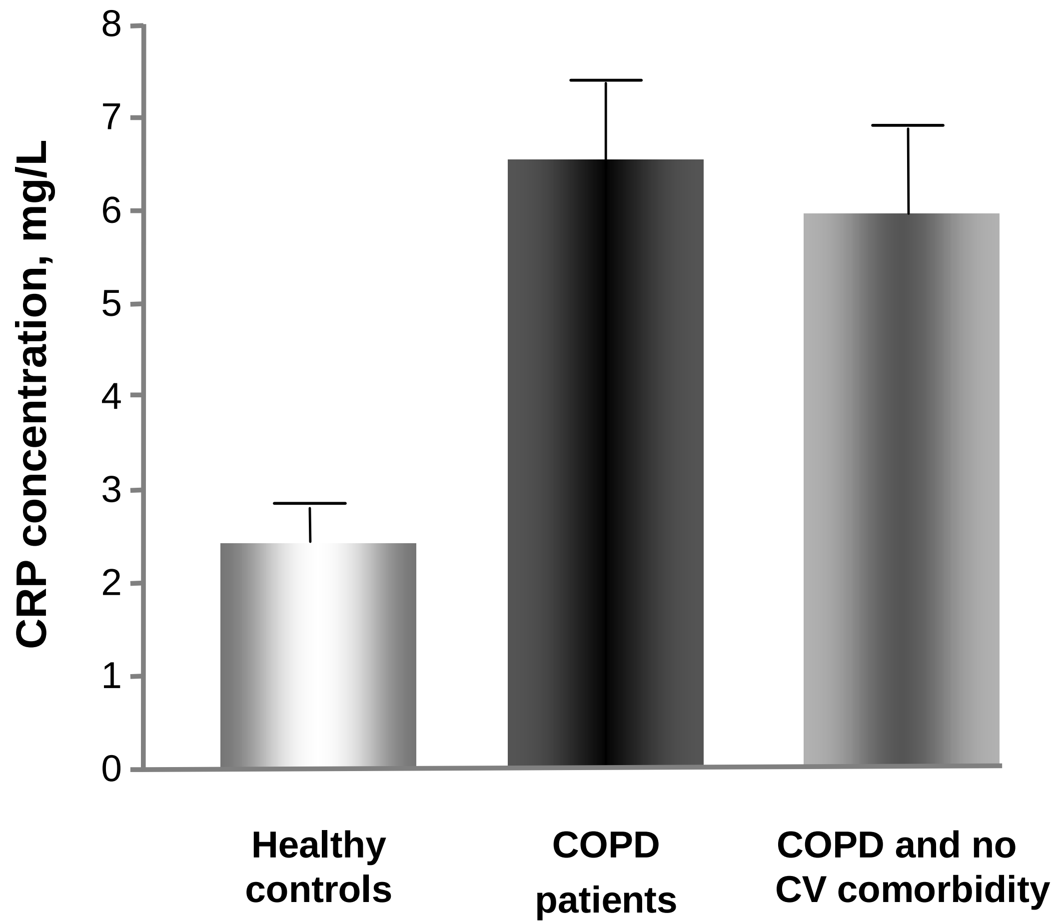
Figure 1.


Reflected wave
Forward wave
SYSTOLIC PRESSURE
Augmentation pressure (AP)
PULSE PRESSURE (PP)
MEAN ARTERIAL
PRESSURE
Dicrotic notch
DIASTOLIC PRESSURE
Time to wave reflection (Tr)


Augmentation pressure, mmHg
20
18
16
14
12
10
8
6
4
2
0
Healthy controls
COPD patients
COPD and no CV comorbidity


Time to wave reflection, ms
140
138
136
134
132
130
128
126
Healthy controls
COPD patients
COPD and no CV comorbidity


CRP concentration, mg/L
8
7
6
5
4
3
2
1
0
Healthy controls
COPD patients
COPD and no CV comorbidity