Bratisl Lek Listy 2011; 112 (1)
24 – 28

CLINICAL STUDY

Carotid intima-media thickness in patients with chronic obstructive pulmonary disease

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Abstract: *Objective:* Chronic obstructive pulmonary disease (COPD) is associated with increased cardiovascular morbidity and mortality. Several large population-based cohort studies identified an association between reduced lung function and increased intima-media thickness (IMT). Nevertheless, a vast majority of subjects in these studies did not suffer from COPD and thus it remains unclear whether IMT differs among various stages of COPD severity. The aim of the present pilot study was to evaluate IMT in central European patients with moderate, severe and very severe COPD.
Methods: In forty-nine patients (34 men, 15 women; mean age 66.1±10.9 years) with COPD, the combined thickness of intima and media layers of the common carotid arteries was measured using B-mode ultrasound imaging.
Results: Increased cardiovascular disease risk as evidenced by carotid IMT values greater or equal to 75th percentile were present in 14 (28.6 %), whereas IMT hypertrophy (IMT values greater or equal 0.80 mm) was present in 24 (49.0 %) of patients. Average IMT in the entire cohort was 0.85±0.21 mm, with no significant differences from stage II to stages III and IV of COPD.
Conclusion: Present results indicate a high prevalence of IMT hypertrophy and increased cardiovascular disease risk as assessed by carotid ultrasonography in COPD patients with a broad spectrum of airway obstruction severity. The lack of differences in carotid IMT between various stages of lung impairment severity suggests that atherosclerosis starts early in the course of COPD. Therefore, the need to screen patients for the presence of concomitant atherosclerosis in early stages of COPD severity may be warranted *(Tab. 2, Ref. 33).*
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Key words: COPD, atherosclerosis, ultrasound, intima-media thickness, cardiovascular risk.

Over the past 15 years, a considerable effort has been devoted to increase the understanding and awareness of both, the pulmonary and extrapulmonary features of chronic obstructive pulmonary disease (COPD). According to WHO, COPD has been identified as a world epidemic that is expected to move to the 3rd leading cause of mortality in 2020 (1). The international initiative GOLD (Global Initiative for Chronic Obstructive Lung Disease) has defined COPD as a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients (2). The pathogenesis and clinical manifestations of COPD are not restricted to pulmonary inflammation and airway remodeling (2). Among the extrapulmonary effects of COPD, the best characterized comorbidities include cardiovascular diseases, cachexia and muscle dysfunction, osteoporosis, anemia, chronic anemia, clinical depression and anxiety (3, 4).

The spectrum of cardiovascular sequelae of COPD includes right ventricular dysfunction, pulmonary hypertension, coronary artery disease and arrhythmias (5).

Epidemiological studies suggest that COPD increases the risk of CVD two- to threefold (6). Indeed, independently of age, gender and smoking history, the patients with COPD are at a significantly higher risk of death from myocardial infarction (6, 7). Recent studies suggest that the mechanisms linking the increased CVD risk and COPD are related to persistent low-grade systemic inflammation (8). Nevertheless, although close pathogenetic and clinical relationships between COPD and atherosclerosis have been postulated, the scientific data linking the two conditions are surprisingly limited (9). In the Atherosclerosis Risk in Communities (ARIC) Study, a decrease in forced expiratory volume in one second (FEV_1) was associated with a decrease in ankle-brachial index and increase in carotid intimal–medial thickness (IMT) (10,

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Support: Agency of the Ministry of Education of the Slovak Republic for the Structural Funds of the European Union, Operational Programme Research and Development (OP R&D), Contract No: 005/2009/2.1/OPR&D.

Acknowledgements: The work was supported by Agency of the Ministry of Education of the Slovak Republic for the Structural Funds of the European Union, Operational Programme Research and Development (OP R&D), Contract No: 005/2009/2.1/OPR&D.

11). In the population-based cohort of 'Men Born in 1914', the risks of developing an asymptomatic leg and carotid atherosclerosis were related to the degree of ventilatory capacity (12). Recently, Iwamoto et al. (9) reported cases of exaggerated subclinical atherosclerosis assessed by IMT in middle-aged smokers with airflow limitation. The authors suggest that the subjects who are susceptible to COPD may also be susceptible to vascular atherosclerosis. Nevertheless, all mentioned studies analyzed subclinical atherosclerosis in large cohorts in which the majority of subjects did not suffer from COPD (9–12). Therefore, it remains unanswered whether IMT differs among various stages of COPD severity. If atherosclerotic changes start early in the course of COPD, high prevalence of subclinical atherosclerosis would be present as early as in Stage II of COPD. Importantly, the understanding of the timing of the course of atherosclerotic changes in carotid arteries in patients with COPD might become valuable for clinical management including the screening strategies and early intervention in these patients. Therefore, the aim of the present pilot study was to assess the subclinical atherosclerosis in central European patients with COPD and different severity of airflow limitations.

Methods

According to the American Thoracic Society/European Respiratory Society guidelines (13), patients with the diagnosis of COPD were consecutively recruited to the study from a university hospital setting. The information on Romany background was retrieved by self-identification of the patients and their relatives. Exclusion criteria included respiratory disorders other than COPD, pulmonary embolism, thromboembolic disease, heart failure, malignancy, systemic autoimmune disorders, infectious diseases and recent surgery, as well as severe endocrine, hepatic or renal diseases. The study had local ethics committee approval, and all subjects gave written consent to the study.

Pulmonary function was evaluated with body plethysmography (Ganshorn, Germany); all testing was performed according to the European Respiratory Society standards in patients in a sitting position at the same time of the day and by the same technician in order to maintain consistency of the technique. Three technically acceptable measurements were performed in each patient while the highest one was included in the analyses.

The combined thickness of the intima and media layers of the common carotid arteries was measured as previously described by using the B mode ultrasound imaging at our laboratory (14). Carotid arteries were scanned bilaterally using a high-resolution ultrasonographic device (AU4 Idea, Esaote Biomedica, Italy) with a 7.5-MHz linear transducer. The examiner was blinded to the results of clinical and biochemical examinations. Intraobserver variability expressed as the correlation coefficient between two repeated measurements of IMT separated by a one-week period was within the acceptable range (r=0.88). The measurements were made on the far walls of the distal CCA over a length of 10 mm proximal to the flow divider in the area where no visible atherosclerotic plaque was present. The mean values from both sides were calculated. These values were termed carotid IMT. Based on previous studies (15), we considered the carotid IMT >0.80 mm reflect the intimal–medial thickening (intimal–medial hypertrophy). Furthermore, the carotid IMT values greater or equal to 75th percentile for the given age, gender and ethnicity (16) were considered indicative of increased CVD risk.

Venous blood for routine haematological and biochemical analyses was drawn by puncturing the antecubital vein under standardized conditions between 7.00 and 8.00 a.m. after an overnight fasting and following 30 minutes of rest at the clinic. Patients were instructed to abstain from smoking and using oxygen as well as to avoid heavy physical activity during the night and morning before blood sample collection. At the time of the collection of venous blood samples, an arterial blood sample was obtained by puncturing the radial artery for blood gas analysis.

Analyses of peripheral leukocyte count were performed using standard techniques. Serum was separated from blood cells by centrifugation at 4000 cycles/min. High-sensitivity serum C-reactive protein levels were assessed by chemiluminiscent immunoassay (Tina-Quant, Roche Diagnostics, Germany). The analytical sensitivity of this C-reactive protein assay is of 0.1 mg/L.

To determine the inter-group differences, one-way analysis of variance (ANOVA) was used for normally distributed variables, and ANOVA on ranks for not normally distributed variables. The prevalence of various variables was compared using the $\div^2$ test. The results are presented as mean ± SD for normally distributed data, and as median (interquartile range) for not normally distributed data. A p value of < 0.05 was considered statistically significant. Analyses were conducted using SPSS for Windows software (version 14.0).

Results

Patient Characteristics

Forty-nine patients with COPD (34 men and 15 women) were enrolled in this study. They were generally late-middle-aged (mean age 66.1±10.9 years) with a mean 23.6±17.4 pack-year history of smoking and a history of 9.9±7.4 years of disease duration (Tab. 1). Twelve (24.4 %) patients in the studied cohort had a Romany background. All patients had the diagnosis of COPD in their case history, and they were using short-acting bronchodilators (salbutamol or ipratropium bromide) to relieve their symptoms. In addition, 35 (71 %) of patients were on long-term treatment with LABA, 33 (67 %) with inhaled corticosteroids, 34 (69 %) with theophyllines, 6 (12 %) with oral corticosteroids, and 5 (10 %) with long-term home oxygen therapy. Coronary heart disease was present in 23 patients (47 %), arterial hypertension in 15 (30.6 %), history of myocardial infarction in 7 (14.2 %), and stroke in 4 (8.2 %). Thirteen patients of the cohort were classified as stage II, twenty-three patients were in stage III, and thirteen patients were in stage IV COPD (17). No differences were observed between the different GOLD stage groups in age, gender, pack-year history of smoking and paO_2 (Tab. 1). In contrast, $paCO_2$ increased from GOLD stage II to stages III and IV (p=0.034).

Compared to the ethnic majority population, patients with Romany background were younger (68.3±9.3 vs 59.7±13.2 years,

Tab. 1. Demographic data, pulmonary function parameters and biochemical variables in patients with COPD.

Variable	Entire cohort	GOLD stage II	GOLD stage III	GOLD stage IV	p value ANOVA
Number of patients, No	49	13	23	13	
Gender, No					
Male	34	8	18	8	;0.521
Female	15	5	5	5	
Age, yr	66.1±11.0	62.2±14.2	68.3±10.0	65.9±7.9	0.300
Packyears (year)	23.6±17.4	14.1±12.8	25.7±20.9	28.8±11.3	0.097
Disease duration (year)	9.9±7.4	5.1±4.9	13.5±7.1*	7.9±6.6	0.005
BMI ($kg.m^{-2}$)	25.9±7.6	26.9±6.9	27.9±7.7	22.0±7.0	0.111
FEV1/FVC, %	50.1 (41.9–61.3)	64.0 (54.5–75.1)	45.0 (41.6–57.8)*	43.0 (33.5–54.3)*	0.001
RV, L	4.4±1.5	3.2±0.9	4.5±1.4*	5.3±1.4*	0.001
RV, %	184.8±57.4	142.4±37.5	181.8±47.7*	236.4±53.5*	0.001
TLC, L	7.1 (4.9–8.4)	6.2 (4.6–7.2)	7.6 (5.5–8.7)	7.3 (6.7–7.8)	0.239
RV/TLC, %	66.0 (56.0–74.8)	54.0 (51.9–56.0)	66.0 (61.8–70.0)*	78.0 (75.3–83.8)*	0.001
pH	7.43±0.05	7.45±0.04	7.42±0.05	7.41±0.03	0.068
paO_2, kPa	8.3±1.6	8.7±2.0	8.1±1.5	8.1±1.6	0.569
$paCO_2$, kPa	5.4±1.3	4.7±0.6	5.4±1.4	6.1±1.5*	0.035
saO_2, %	91.6 (88.0–94.9)	91.7 (85.2–96.0)	91.5 (87.4–94.5)	91.0 (89.0–93.2)	0.861
Cholesterol (mmol/l)	4.9±0.9	5.2±0.7	4.9±1.0	4.5±0.9	0.163
Haemoglobin (g/l)	135.5±17.5	131.5±19.7	137.0±17.8	136.2±15.8	0.690
Leukocytes (x109/l)	9.6±3.8	10.2±8.2	8.3±6.5	9.7±7.0	0.456
Neutrophils (%)	64.7±17.5	68.8±16.9	58.8±18.1	72.4±13.6	0.071
CRP (mg/l)	19.4 (5.0–48.8)	25.1 (5.0–40.2)	14.9 (5.0–37.4)	22.0 (4.0–68.1)	0.931

* $p<0.05$ versus GOLD Stage II

Values given as mean ± SD. BMI = body mass index; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; paCO2 = arterial carbon dioxide partial pressure; paO_2 = arterial oxygen partial pressure

p Value refers to trend from GOLD Stage II, to Stage III and to Stage IV (ANOVA).

Tab. 2. Carotid Intima-Media Thickness (IMT) and the presence of IMT value higher than 75th percentile indicative of increased cardiovascular disease risk in patients with COPD.

	Entire group	GOLD Stage II	GOLD Stage III	GOLD Stage IV	P value
IMT right (mm)	0.83±0.22	0.84±0.14	0.82±0.22	0.85±0.27	0.941
IMT left (mm)	0.86±0.25	0.83±0.23	0.91±0.29	0.81±0.14	0.469
IMT average (mm)	0.85±0.21	0.83±0.18	0.86±0.23	0.82±0.19	0.860
IMT >75th percentile (No)	14	5	6	3	0.642
IMT >0.8 mm (No)	24	5	13	6	0.565

p=0.017), and the proportion of women was higher (7 out of 37 vs 8 out of 12, p=0.004). Nevertheless, no differences were observed between the ethnic majority and Romany patients in the mean BMI (25.3±6.7 vs 27.5±9.4 kg/m^2, p=0.415), disease duration (9.0±7.4 vs 12.5±7.2 years, p=0.210), and pulmonary functions (FEV_1: 41.1±16.8 vs 42.5±22.1 % predicted, p=0.815), residual volume: 192±59 vs 160±44 % predicted, p=0.093).

Carotid Intima-Media Thickness

Increased CVD risk as evidenced by carotid IMT values greater or equal to 75th percentile (16) was present in 14 (28.6 %) of patients. IMT hypertrophy as evidenced by carotid IMT values greater or equal 0.80 mm (15) was present in 24 (49.0 %) of patients. Average IMT in the entire cohort was 0.85±0.21 mm, with no significant differences from stage II to stage III and IV COPD (Tab. 2). No differences were observed in the carotid IMT between the majority and Romany patients (0.87±0.22 vs 0.80±0.14 mm, p=0.341).

Discussion

In the present study, we have demonstrated an extraordinarily high prevalence of IMT hypertrophy (49.0 %) and an increased CVD risk as assessed by carotid ultrasonography in COPD patients with broad spectrum of airway obstruction severity. Several previous large community-based cohort studies suggested a link between the reduced lung function and carotid atherosclerosis (10–12). Nevertheless, to our best knowledge based on a thorough search of medical databases (Cochrane Database of Systematic Reviews, Medline via PubMed, and Google Scholar), no data have been published until now on potential differences in IMT values between the respective stages of COPD severity. Therefore, the results of our pilot study extend beyond the previous findings by suggesting that once airflow limitation is present and COPD criteria met, no significant differences may be observed in IMT values between GOLD Stages II, III and IV of COPD severity.

COPD is a major cause of morbidity and mortality worldwide. Irreversible airflow limitation, both progressive and associated with inflammatory response of the lungs to noxious particles or gases, is a hallmark of the disease while respiratory failure is considered the major cause of death in advanced COPD. The natural course of COPD is complicated by the development of systemic consequences and comorbidities with a detrimental impact on hospitalization and mortality rates in these patients. Indeed, COPD increases the risk of cardiovascular diseases, cachexia, osteoporosis, lung cancer, anemia, anxiety and depression independently of the airway obstruction severity (3, 4). The associations between smoking, obstructive ventilatory impairment, systemic manifestations, and comorbidities in COPD have only recently begun to be studied in depth while future approaches based on recent and evolving research are highly warranted (3).

It has become increasingly evident that independently of age, gender and smoking history, the patients with COPD are at a significantly higher risk of death from myocardial infarction, (6). Importantly, patients with milder COPD have actually a higher chance of dying from a cardiovascular cause than from respiratory insufficiency (18) while cardiovascular events are the leading cause of hospitalization and the second leading cause of mortality surpassed only by lung cancer in patients with mild-to moderate COPD (7). Indeed, in subjects with FEV_1 > 50 % of predicted values, cardiovascular disorders account for approximately 50 % of all hospitalizations and nearly a third of all deaths (7). In patients with GOLD Stages III and IV of the disease (FEV_1 < 50 % of predicted values), the prevailing cause of mortality relates to pulmonary impairment and respiratory failure, whereas cardiovascular events account for approximately 20–25 % of all deaths (19). Hole et al (20) observed that independently of the effects of cigarette smoking, approximately 25 % of all ischemic cardiac deaths in men are attributable to impaired lung function. Interestingly, the risk imposed by hypercholesterolemia in their study was only 21 % in men (20) suggesting that for ischemic cardiac deaths, the reduced lung function imposes a risk similar to that of hypercholesterolemia (4).

The principal cause of coronary heart disease, stroke, and peripheral vascular disease is atherosclerosis (21). The presence of low-grade systemic inflammation in both COPD and atherosclerotic cardiovascular disease could represent one of the key mechanisms driving both pathologies (3). Inflammatory markers such as CRP are associated with increased carotid IMT (22), they predict an incident of cardiovascular disease, and are associated with the presence of subclinical atherosclerosis in general population. In addition, circulatory CRP levels are associated with clinically important outcomes in patients with COPD, and they significantly relate not only to the poor performance in six-minute walk distance test (23) but also to the increased mortality in such patients (24). COPD-related increases in systemic markers of oxidative stress may contribute further to the increase in atherosclerotic risk. Indeed, in our previous studies, we have shown a close association between systemic inflammation and systemic oxidative stress reflected by erythrocytic glutathione peroxidase in patients with acute exacerbations of COPD (25), and an association between parameters of oxidative stress and lung functions (26). Interestingly, in patients with obstructive sleep apnea, the severity of oxygen desaturation appeared to be the best predictor of carotid IMT (27). Nevertheless, the roles of COPD-related systemic inflammation, hypoxia and oxidative stress in the progression of carotid atherosclerosis need to be studied in more details in the future.

Subclinical carotid atherosclerosis as evidenced by increased IMT was reported to correlate with coronary and intracranial atherosclerosis, as well as to predict the future cardiovascular events (28–31). In both, clinical and research practice, the assessment of carotid IMT using the B-mode ultrasonography represents a well-validated method for evaluating the carotid atherosclerosis (16, 32). Previously, several studies have suggested a relationship between carotid IMT values and pulmonary function in large population-based cohorts. In a population-based cohort of 'Men Born in 1914' in Sweden, the risk of developing an asymptomatic leg and carotid atherosclerosis was related to the degree of ventilatory capacity (12). In another study on elderly subjects free of coronary heart disease and stroke, the peak expiratory flow predicted the development of carotid atherosclerosis during a four-year follow-up (33). Furthermore, in their large-scale ARIC Study, Schroder et al (10) observed complex relationships between FEV_1 and atherosclerotic vascular disease. Decreased FEV_1 was associated with increased IMT in the full cohort of 14,000 adult participants. However, adjustments for traditional CVD risk factors attenuated this association, eliminating it in never-smokers. In addition, plaque formation was not associated with FEV_1. Further analyses of the ARIC cohort suggested that the relationship between FEV_1 and atherosclerotic risk might be stronger in women than in men (11). Recently, Iwamoto et al. (9) evaluated the signs of subclinical atherosclerosis in middle-aged smokers and found a significantly increased IMT in smokers with airflow limitation when compared to control smokers and control never-smokers. Subsequently, these authors suggested that atherosclerotic changes in the carotid arteries start early in the course of COPD. Nevertheless, in their group of smokers with airflow limitation, the mean FEV_1 of 83 % was predicted, and the mean FEV_1/FVC ratio was 65 %, suggesting that patients with severe COPD were not included in their analyses. Importantly, our results on high prevalence of IMT hypertrophy in the central European cohort of COPD patients with various stages of COPD severity on one hand, and no significant differences between the carotid IMT values between the various groups of patients with different COPD severity strongly support the thesis suggested by Iwamoto et al (9). Despite the limitation of the present analyses based on testing a relatively small sample of COPD patients, our study is clinically relevant and provides supportive evidence that atherosclerosis is likely to represent an early systemic manifestation of COPD.

In conclusion, our pilot study demonstrated the early signs of subclinical atherosclerosis as evidenced by carotid IMT hypertrophy in 49 %, and increased the CVD risk as indicated by carotid IMT values greater or equal to 75th percentile of age, race, and gender values (16) in 28.6 % of patients with COPD. The lack of differences in carotid IMT between various stages of COPD severity suggests that atherosclerosis of carotid arteries starts early in the course of COPD. Although the mechanisms responsible for increased

atherosclerotic risk in COPD have not been entirely elucidated so far, as well as despite the fact that they did not represent the objective of the present study, our results may have important clinical implications by suggesting the need to screen patients for the presence of concomitant atherosclerosis in all stages of COPD severity.

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Received October 26, 2009.
Accepted October 8, 2010.