ORIGINAL ARTICLE

Peripheral Artery Disease and Its Clinical Relevance in Patients with Chronic Obstructive Pulmonary Disease in the COPD and Systemic Consequences–Comorbidities Network Study

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Abstract

Rationale: Knowledge about the prevalence of objectively assessed peripheral artery disease (PAD) and its clinical relevance in patients with chronic obstructive pulmonary disease (COPD) is scarce.

Objectives: We aimed to: (*1*) assess the prevalence of PAD in COPD compared with distinct control groups; and (*2*) study the association between PAD and functional capacity as well as health status.

Methods: The ankle–brachial index was used to diagnose PAD (ankle–brachial index $\leqslant 0.9$). The 6-minute-walk distance, health status (St. George's Respiratory Questionnaire), COPD Assessment Test, and EuroQol-5-Dimensions were assessed in patients enrolled in the German COPD and Systemic Consequences–Comorbidities Network cohort study. Control groups were derived from the Study of Health in Pomerania.

Measurements and Main Results: A total of 2,088 patients with COPD (61.1% male; mean [SD] age, 65.3 [8.2] years, GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages I–IV: 9.4, 42.5, 37.5, and 10.5%, respectively) were included, of which 184 patients (8.8%; GOLD stage I–IV: 5.1, 7.4, 11.1, and 9.5%, respectively, vs. 5.9% in patients with GOLD stage 0 in the COPD and Systemic Consequences–Comorbidities Network) had PAD. In the Study of Health in Pomerania, PAD ranged from 1.8 to 4.2%. Patients with COPD with PAD had a significantly shorter 6-minute-walk distance (356 [108] vs. 422 [103] m, $P < 0.001$) and worse health status (St. George's Respiratory Questionnaire: 49.7 [20.1] vs. 42.7 [20.0] points, $P < 0.001$; COPD Assessment Test: 19.6 [7.4] vs. 17.9 [7.4] points, $P = 0.004$; EuroQol-5-Dimensions visual analog scale: 51.2 [19.0] vs. 57.2 [19.6], $P < 0.001$). Differences remained significant after correction for several confounders.

Conclusions: In a large cohort of patients with COPD, 8.8% were diagnosed with PAD, which is higher than the prevalence in control subjects without COPD. PAD was associated with a clinically relevant reduction in functional capacity and health status.

Keywords: chronic obstructive pulmonary disease; comorbidities; peripheral vascular disease; health status; functional capacity

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At a Glance Commentary

Scientific Knowledge on the Subject: Peripheral artery disease (PAD) is associated with morbidity and mortality. However, many individuals with PAD are asymptomatic and unaware of the disorder. The ankle–brachial index (ABI) is not only a common diagnostic measure for PAD but also an indicator of atherosclerosis at other vascular sites. To date, knowledge on the prevalence of PAD as assessed by ABI and the associations of objectively assessed PAD with functional capacity and health status in a large cohort of patients with chronic obstructive pulmonary disease (COPD) is scarce.

What This Study Adds to the Field: This study shows that, in a large cohort of patients with COPD of all degrees of severity, 8.8% were diagnosed with PAD (ABI $\leq$ 0.9), which is higher than the prevalence in control subjects without COPD. Of note, more than two-thirds of these patients did not report PAD in their medical history. Patients with PAD showed a worse functional capacity and worse health status compared to those without PAD. These differences exceeded the thresholds commonly considered as clinically relevant.

Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic disease that is primarily characterized by progressive airflow limitation (1). Beyond respiratory impairment, patients with COPD often suffer from coexisting diseases, the majority (up to 98%) showing one or more comorbidities (2, 3). Therefore, the interest in understanding COPD as a complex multisystem disease is increasing (4).

Because of their direct impact on survival (5–7), cardiovascular diseases are probably the most important coexisting diseases in COPD (1). Peripheral artery disease (PAD) is an atherosclerotic process that refers to the occlusion of the arteries in the lower limbs (8). PAD is a risk factor for other cardiovascular diseases, and is often described as a "silent killer," as a high number of individuals with PAD are asymptomatic and unaware of the disorder (9).

The ankle–brachial index (ABI) is the ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery (10). The ABI is not only a common diagnostic measure for PAD, but also an indicator of atherosclerosis at other vascular sites (10). This renders the ABI a good prognostic marker for cardiovascular events (10), even beyond traditional risk calculations, such as the Framingham risk score (11).

However, knowledge about the prevalence and clinical relevance of objectively assessed PAD in patients with COPD is scarce. Therefore, we aimed to determine the prevalence of PAD in a large cohort of patients with COPD compared with patients with a similar risk profile, but without fixed airflow obstruction (GOLD [Global Initiative for Chronic Obstructive Lung Disease] stage 0), matched control subjects without COPD, and individuals with an airflow limitation in two epidemiological cohorts. Furthermore, we aimed to study the associations between PAD and functional capacity, as well as disease-specific and generic health status in a large cohort of patients with COPD.

Some of the results have been previously reported in the form of abstracts (12–14).

Methods

The patient cohort is comprised of 2,741 patients who were enrolled in the German COSYCONET (COPD and Systemic Consequences–Comorbidities Network) cohort study, which is a multicenter, longitudinal, prospective, observational study focusing on the interaction of lung disorder and comorbidities over time. Patients were recruited from September 2010 to December 2013 in 31 study centers throughout Germany, and were eligible if they were 40 years of age or older and had a diagnosis of COPD or symptoms of chronic bronchitis (15). Patients with missing lung function data, unclassified patients, patients with α_1-antitrypsin deficiency, and patients with missing ABI measurement were excluded from the current analyses, resulting in a sample of 2,425 patients. Of these patients, 13.9% (n = 337) had a postbronchodilator ratio of FEV_1/FVC 70% or greater, but: (*1*) had a doctor diagnosis of chronic bronchitis and/or (*2*) reported 3 points or greater on the COPD Assessment Test (CAT) item regarding symptoms of cough and/or (*3*) reported 3 points or greater on the CAT item regarding symptoms of phlegm. These individuals were classified as patients "at risk" for COPD or GOLD stage 0 according to previously published guidelines (16). In the primary analyses, evaluating the associations between PAD and functional capacity as well as health status in patients with COPD, patients with GOLD stage 0 were excluded, leading to an analysis of a COPD population of 2,088 patients.

The control groups were based on data from two independent epidemiological cohorts of SHIP (Study of Health in Pomerania) conducted in northeastern Germany. SHIP is a population-based survey investigating 4,308 eligible subjects randomly selected from population registries stratified by age and sex to reach the most representative population as possible during its baseline examinations (SHIP S0). PAD and lung function investigations are based on the second follow up (SHIP S2) between 2008 and 2012, as well as on a second independent baseline cohort (SHIP-TREND-0) consisting of 4,420 individuals. Details have been presented previously (17). With a case–control approach, a 1:1 individual

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random matching by sex and age (±5 yr) was used to match COSYCONET patients with control subjects without COPD to compare PAD prevalence. Control subjects without COPD were selected from the SHIP population after exclusion of subjects under 40 years of age, with a prebronchodilator ratio of FEV_1/FVC less than 0.7, FEV_1 less than 85% predicted, or use of inhalation medications (Anatomical Therapeutic Chemical code R03). In total, for 1,708 COSYCONET patients with COPD (GOLD stages I–IV), control subjects without COPD could be matched (*see* Table E1a in the online supplement). The selection of control subjects without COPD was further extended by also including subjects with a FEV_1 less than 85% predicted and matching for smoking status (with a case–control approach, a 1:1 individual random matching; *see* Tables E1b and E1c, respectively). In an additional analysis, we determined the prevalence of PAD in subjects with airflow obstruction (FEV_1/FVC < 0.7) in SHIP (*see* Table E2).

In COSYCONET, demographics and clinical characteristics were assessed at the participating study centers. Postbronchodilator spirometry (45 min after administration of 400 μg salbutamol and 80 μg ipratropium bromide) was performed according to American Thoracic Society/European Respiratory Society recommendations using established reference values (18). Diffusing capacity of the lung for carbon monoxide (D_{LCO}; single breath, mean value of two measurements) was assessed. Predicted values were calculated using previously published reference values (19). Patients were classified according to the spirometric criteria of GOLD (18) and the GOLD groups A–D criteria (1). The CAT was used to classify patients into low-symptom groups A/C or high-symptom groups B/D. Comorbidities (e.g., hypertension, diabetes, PAD; assessment by a structured interview), as well as the levels of highly sensitive C-reactive protein, cholesterol, and triglycerides, were assessed and included as possible risk factors for PAD in the current study.

PAD

PAD was objectively diagnosed using the ABI, which represents the ratio of ankle systolic pressure to brachial systolic pressure. In the COSYCONET cohort, systolic pressures were measured by a sphygmomanometer (VASCassist; iSYMED GmbH, Butzbach, Germany) on the left and right side in supine position. The lowest ABI value was selected for analyses, as an ABI of 0.90 or lower in either leg is considered evidence of PAD (20). In SHIP, systolic blood pressure was measured with a Dopplex D900 (Huntleigh Healthcare Ltd., Cardiff, UK) doppler ultrasound probe and a blood pressure cuff (Welch Allyn, Skaneateles Falls, NY) in both arms and both ankles (anterior and posterior tibial artery) in supine position. A cutpoint of an ABI of 0.90 or less was used to define PAD (10). Further details are provided in the online supplement.

Clinical Outcome Measures

Functional capacity was assessed by the 6-minute-walk distance (6MWD), which was determined according to previous guidelines (21). The minimal clinically important difference (MCID) of the 6MWD is 30 m (22). Predicted values were calculated using previously published reference values (23).

Disease-specific health status was assessed using the COPD-specific St. George's Respiratory Questionnaire (SGRQ) for COPD (24) and the CAT (25). The SGRQ provides symptom, activity, and impact domain scores and a total score, all ranging from 0 to 100 points. The MCID of SGRQ is 4 points for each domain score and the total score (26). The CAT consists of eight items and provides a total score ranging from 0 to 40. The MCID of the CAT is 2 points (27). Higher scores represent worse disease-specific health status in both questionnaires.

Generic health status was assessed using the EuroQol-5-Dimensions (EQ-5D-3L) instrument. It consists of five items (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) with three levels (no problems, some problems, and extreme problems) and a visual analog scale (VAS) for valuing health on a rating scale from 0 (worst imaginable health state) to 100 (best imaginable health state). Utility scores can be obtained from the five items by weighting the answers according to a weighting scheme. The German Time Trade Off tariff was used to calculate utility scores ranging from 0 to 1, with higher values indicating better health (28). The MCID of 8 points for the EQ-5D VAS has been proposed for patients with moderate to severe COPD (29). A MCID for the EQ-5D-3L utility score is not yet established, but may range between 0.08 and 0.10 according to studies in patients without COPD (30–32). In a previous analysis of the COSYCONET data set comparing disease-specific and generic health status instruments, the SGRQ showed the best discrimination between COPD grades, and was less influenced by self-reported comorbidities, whereas the EQ-5D-3L utility had a higher weight on self-reported comorbid conditions (33).

Statistical Analysis

The current analysis is a cross-sectional analysis of the COSYCONET cohort study (visit 1). Data are presented as mean (±SD) or median (quartile) values, depending on the distribution of the data. Characteristics were compared between patients with and without PAD using an independent sample *t* test or Mann-Whitney *U* Test, as appropriate. Categorical variables were compared using single-proportion χ^2 tests. Logistic regression analyses were performed to detect the association between PAD and age, sex, smoking status, D_{LCO} % predicted, GOLD stage, hypertension, diabetes, highly sensitive C-reactive protein, and triglycerides. A further logistic model, including patients with GOLD stage 0, was also performed. Possible confounders were identified by univariate analyses (i.e., measures that significantly differ between patients with and without PAD have been included in the multivariate model). Skewed data were log transformed beforehand. General linear models were used to compare functional capacity (i.e., 6MWD) between patients with and without PAD, correcting for possible confounders (age, sex, height, weight, D_{LCO} % predicted, GOLD stage, smoking status, hypertension, myocardial infarction, and angina pectoris), and health status between patients with and without PAD, correcting for possible confounders (age, sex, D_{LCO} % predicted, GOLD stage, smoking status, hypertension, myocardial infarction, and angina pectoris). Statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL) and SAS 9.3 and 9.4 (SAS Institute Inc., Cary, NC). Figures were constructed using GraphPad Prism (GraphPad Software, Inc., La Jolla, CA). Statistical significance was set at *P* less than or equal to 0.05.

Results

On average, patients with COPD were 65 years old and had moderate to severe airflow limitation (Table 1). Totals of 8.3, 29.8, 4.7, and 57.2% of the patients were classified in GOLD groups A, B, C, and D, respectively.

Prevalence of PAD

PAD (ABI ⩽ 0.9) was detected in 8.8% of the patients with COPD (n = 184). Of these, 65.8% did not report PAD in their medical history.

PAD was detected in 5.9% of the patients with GOLD stage 0 (n = 20). Of these, 55.0% did not report PAD in their medical history.

In age- and sex-matched control subjects without COPD, PAD was detected in 1.8% compared with 8.5% in matched patients with COPD GOLD I–IV (*see* Table E1a). Including control subjects with worse lung function (i.e., $FEV_1 < 85\%$ predicted; *see* Table E1b) and those who were matched for smoking status (*see* Table E1c) increased the prevalence of PAD in the control group to 2.0 and 2.6%, respectively. Of note, the control subjects with PAD had a higher body mass index (BMI), a higher prevalence of obesity and diabetes, and higher levels of triglycerides, but fewer pack-years of smoking and less-frequent hypertension than the age- and sex-matched patients with COPD (*see* Tables E1a–E1c). A further analysis in subjects with mild airflow limitation (FEV_1/FVC, 0.64; FEV_1, 80.2% predicted) in the SHIP cohorts revealed a PAD prevalence of 4.2% (*see* Table E2). Figure 1 presents the prevalence of these groups.

The frequency distribution of ABI values stratified by GOLD 0, GOLD stages, and GOLD groups is shown in Figure E1. Figure 2 shows the prevalence of PAD stratified by GOLD 0 and GOLD stages I–IV and GOLD groups A–D. The proportion of patients with PAD differs between GOLD stages (GOLD 0/I/II/III/IV: 5.9/5.1/7.4/11.1/9.6%, $P = 0.006$) and GOLD groups (GOLD 0/A/B/C/D: 5.9/5.2/7.1/7.1/10.3%, $P = 0.015$).

In patients with COPD, PAD was independently associated with greater age, being a current smoker, impaired diffusion capacity, higher levels of triglycerides, hypertension, and diabetes (Table 2). Independent predictors remained comparable when patients with GOLD stage 0 were included (*see* Table E4).

Relation to Outcome Measures

Patients with COPD and comorbid PAD were older and had worse lung function compared with those patients with COPD without PAD. Furthermore, a higher proportion of patients with COPD with PAD was male, current smokers, and classified as GOLD III patients (Table 1). Descriptive characteristics for patients with GOLD stage 0 stratified by PAD are shown in Table E3.

Patients with PAD had a worse functional capacity, as assessed with the

Table 1. Baseline Characteristics of Patients with Chronic Obstructive Pulmonary Disease Stratified by Peripheral Artery Disease

Characteristic	Whole Group (*n = 2,088*)	Patients with PAD (ABI ⩽ 0.9) (*n = 184*)	Patients without PAD (ABI > 0.9) (*n = 1,904*)
Age, yr	65.3 (8.2)	68.5 (7.0)*	65.0 (8.2)
Male, n (%)	1276 (61.1)	131 (71.2)*	1145 (60.1)
Smoking status, n (%)†			
Never smoker	114 (5.5)	4 (2.2)*	110 (5.8)
Current smoker	550 (26.3)	64 (34.8)*	486 (25.5)
Former smoker	1424 (68.2)	116 (63.0)	1308 (68.7)
Pack-years‡	n = 1,960	n = 179	n = 1,781
	44.0 (25.5–67.5)	45.0 (23.4–72.0)	44.0 (25.5–67.5)
BMI, n (%)	n = 2,087	n = 184	n = 1,903
<18.5 kg/m^2	74 (3.5)	8 (4.3)	66 (3.5)
18.5–25.0 kg/m^2	758 (36.3)	68 (37.0)	690 (36.3)
25.0–30.0 kg/m^2	772 (37.0)	69 (37.5)	703 (36.9)
>30.0 kg/m^2	483 (23.1)	39 (21.2)	444 (23.3)
FEV_1, L‡	1.4 (1.1–1.9)	1.3 (1.0–1.7)*	1.5 (1.1–2.0)
FEV_1, % predicted	52.9 (18.7)	48.4 (17.5)*	53.4 (18.8)
FEV_1/FVC, %‡	52.2 (43.4–60.9)	49.6 (41.9–60.4)	52.3 (43.4–60.9)
D_{LCO}	n = 1,973	n = 176	n = 1,797
	4.5 (1.9)	4.0 (1.9)*	4.6 (1.9)
D_{LCO}, % predicted	n = 1,973	n = 176	n = 1,797
	52.9 (20.8)	47.5 (20.2)*	53.5 (20.8)
GOLD stage, n (%)			
I	197 (9.4)	10 (5.4)	187 (9.8)
II	887 (42.5)	66 (35.9)	821 (43.1)
III	784 (37.5)	87 (47.3)*	697 (36.6)
IV	220 (10.5)	21 (11.7)	199 (10.5)
mMRC dyspnea score, n (%)	n = 2,068	n = 183	n = 1,885
0	168 (8.1)	11 (6.0)	157 (8.3)
1	911 (44.1)	62 (33.9)*	849 (45.0)
2	589 (28.5)	50 (27.3)	539 (28.6)
3	377 (18.1)	53 (29.0)*	324 (17.2)
4	23 (1.1)	7 (3.8)*	16 (0.8)
ABI‡	1.2 (1.1–1.2)	0.8 (0.7–0.9)*	1.2 (1.1–1.2)
hsCRP, mg/L‡	n = 2,065	n = 182	n = 1,883
	4.5 (2.0–7.3)	5.0 (2.2–9.1)*	4.3 (2.0–7.1)
Triglycerides, mg/dl‡	n = 2,061	n = 181	n = 1,880
	115.0 (84.0–168.9)	125.0 (93.6–183.8)*	114.0 (83.0–167.6)
Cholesterol, mg/dl	n = 2,064	n = 181	n = 1,883
	216.2 (44.0)	211.2 (44.7)	216.6 (43.9)
Hypertension, n (%)	1171 (56.1)	131 (71.2)*	1040 (54.6)
Diabetes, n (%)	n = 2,087	n = 184	n = 1,903
	276 (13.2)	38 (20.7)	238 (12.5)

Definition of abbreviations: ABI = ankle–brachial index; BMI = body mass index; D_{LCO} = diffusing capacity of the lung for carbon monoxide; GOLD = Global Initiative for Chronic Obstructive Lung Disease; hsCRP = highly sensitive C-reactive protein; mMRC = modified Medical Research Council scale; PAD = peripheral artery disease.

Values are expressed as mean (SD), unless otherwise indicated.

*$P \leqslant 0.05$ compared to patients without PAD.

†Patients with missing data on smoking status (n = 4) were classified as "former smokers."

‡Nonparametric tests were used owing to skewed data; values expressed as median (interquartile range).

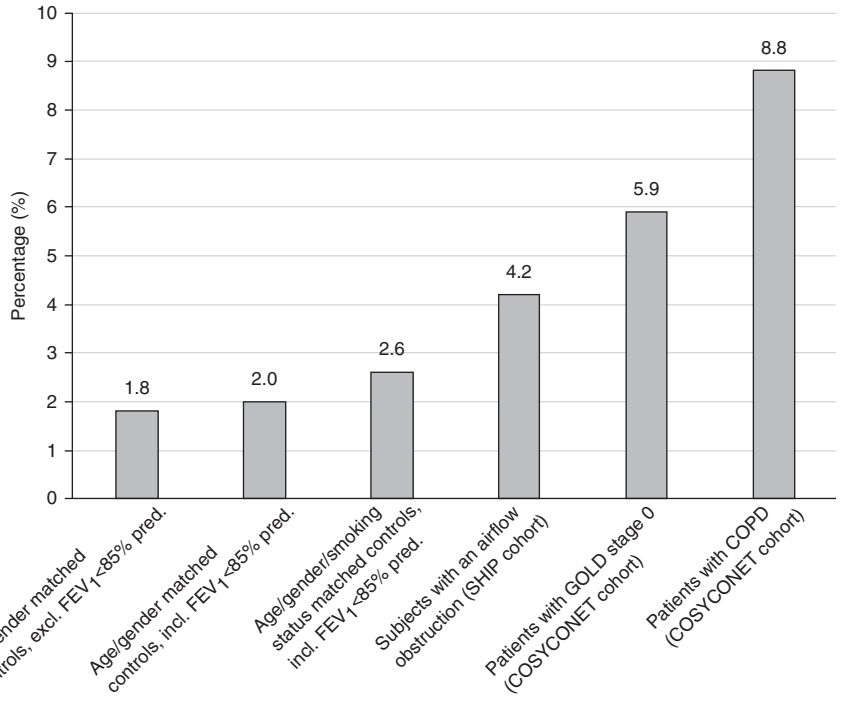

Figure 1. Prevalences of peripheral artery disease in patients with chronic obstructive pulmonary disease (COPD) and several control groups. COSYCONET = COPD and Systemic Consequences–Comorbidities Network; GOLD = Global Initiative for Chronic Obstructive Lung Disease; SHIP = Study of Health in Pomerania.

6MWD (356 [108] vs. 422 [103] m, $P < 0.001$) compared with those without PAD (Figure 3a, Table 3). Accordingly, 6MWD in terms of % predicted values was lower in patients with PAD compared with those without PAD (56.8 [17.0]% predicted vs. 66.3 [16.1]% predicted, $P < 0.001$). The differences in 6MWD remained significant after correction for possible confounders (Table 3) and inclusion of patients with GOLD stage 0 (Table E5).

Furthermore, patients with PAD showed a worse disease-specific health status, as assessed with SGRQ domain scores and total score, with most pronounced differences in SGRQ activity (67.4 [22.9] vs. 57.0 [25.9] points, $P < 0.001$) and SGRQ total score (49.7 [20.1] vs. 42.7 [20.0] points, $P < 0.001$) (Figure 3b, Table 3). Similarly, the CAT score was significantly higher in patients with PAD (19.6 [7.4] vs. 17.9 [7.4] points, $P = 0.004$). In addition, generic health status was more impaired in patients with PAD (e.g., EQ-5D VAS: 51.2 [19.0] vs. 57.2 [19.6] points, $P \leq 0.001$). Specifically, a higher proportion of patients with PAD more frequently reported "some problems" or "severe problems" of mobility (55.4 vs. 38.7%, $P < 0.001$), self-care (22.3 vs. 14.4%, $P = 0.004$), and usual activity (58.7 vs. 50.3%, $P = 0.03$) compared with those without PAD. The differences in disease-specific and generic health status scores remained significant after correction for possible confounders (except for SGRQ symptom score; Table 3) and inclusion of patients with GOLD stage 0 (Table E5).

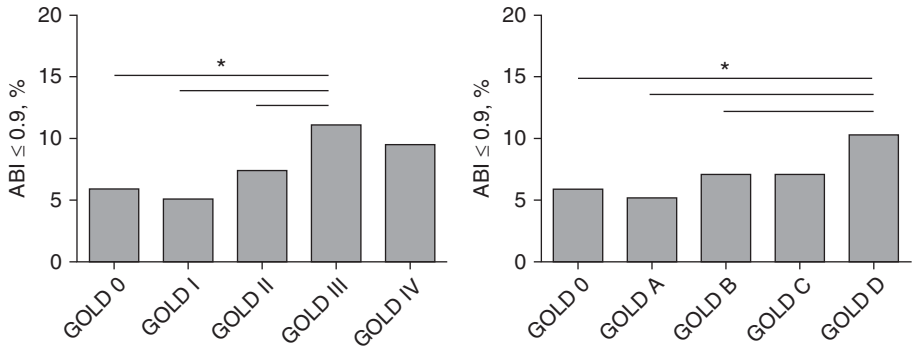

Figure 2. Prevalence of peripheral artery disease stratified by GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages and GOLD groups. ABI = ankle–brachial index. *$P \leq 0.05$.

Discussion

In a large cohort of patients with COPD of all degrees of severity, 8.8% were objectively diagnosed with PAD. Of note, more than two-thirds of these patients did not report PAD in their medical history. Patients affected by PAD showed a clinically meaningful worse functional capacity and health status compared with those without PAD.

Prevalence

The currently available studies regarding the prevalence of PAD in patients with COPD are rather limited, and do not allow us to draw firm conclusions. In a Taiwanese cohort of 427 patients with COPD, 8% of the patients were identified with asymptomatic PAD (34). Although the severity stages of COPD in this Taiwanese cohort were comparable to those in our cohort, the generalizability of these data is difficult, as almost exclusively male patients (98%) were enrolled in this single-center study. Other reported frequencies of an ABI less than 0.9 in COPD have been derived from smaller, single-center studies, and range up to 37% (35–37), with the highest prevalence of 37% in patients hospitalized for an exacerbation of COPD (37). To the best of our knowledge, there are no studies available so far that compared the prevalence of objectively diagnosed PAD in COPD with control subjects without COPD. The current article shows that the prevalence of PAD in COPD is higher than the prevalence in subjects without COPD, even after controlling for smoking status, which is known to substantially affect the

Table 2. Independent Predictors of Peripheral Artery Disease in Patients with Chronic Obstructive Pulmonary Disease Global Initiative for Chronic Obstructive Lung Disease Stages I–IV

Covariates	Exp(B)	95% CI for HR		*P* Value
		Lower	Upper	
Age, yr	1.072	1.047	1.097	**<0.001**
Sex (male), n	1.311	0.904	1.902	0.153
Smoking status, n				
Current smoker	5.928	1.757	20.003	**0.004**
Former smoker	2.770	0.843	9.099	0.093
GOLD, n				
II	1.143	0.562	2.325	0.713
III	1.714	0.824	3.566	0.150
IV	1.624	0.650	4.061	0.300
D_{LCO}, % predicted	0.987	0.977	0.997	**0.009**
hsCRP, mg/L*	1.089	0.954	1.243	0.208
Triglycerides, mg/dl*	1.470	1.077	2.007	**0.015**
Hypertension, n	1.621	1.133	2.319	**0.008**
Diabetes, n	1.518	1.003	2.299	**0.048**

Definition of abbreviations: CI = confidence interval; D_{LCO} = diffusing capacity of the lung for carbon monoxide; Exp(B) = exponentiation of the B coefficient; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = hazard ratio; hsCRP = highly sensitive C-reactive protein.
Logistic regression with dependent variable ankle–brachial index (ABI) ⩽ 0.90 (n = 173 with ABI ⩽ 0.90 vs. n = 1,763 with ABI > 0.90). Never smokers as well as GOLD I were selected as reference categories. Bold values represent significant results.
*Log-transformed owing to skewed data.

relationship between COPD and cardiovascular disease (38, 39). Notably, the nonobstructive control subjects had a higher risk profile for PAD than the patients with COPD according to their BMI and the prevalence of obesity (BMI > 30 kg/m^2), diabetes, and hypertriglyceridemia, which, in turn, underlines the important role of COPD as a potential, and so far underestimated, risk factor for PAD. We found the highest prevalence of PAD with 4.2% in the control subjects with mild airflow obstruction, which is close to the prevalence of PAD of 5.1% in our GOLD stage I patients.

Due to its size, the current study provided enough power to study multiple relationships. PAD was associated with greater age, current smoking status, higher levels of triglycerides, hypertension, and diabetes, all of which are established risk factors for cardiovascular disease.

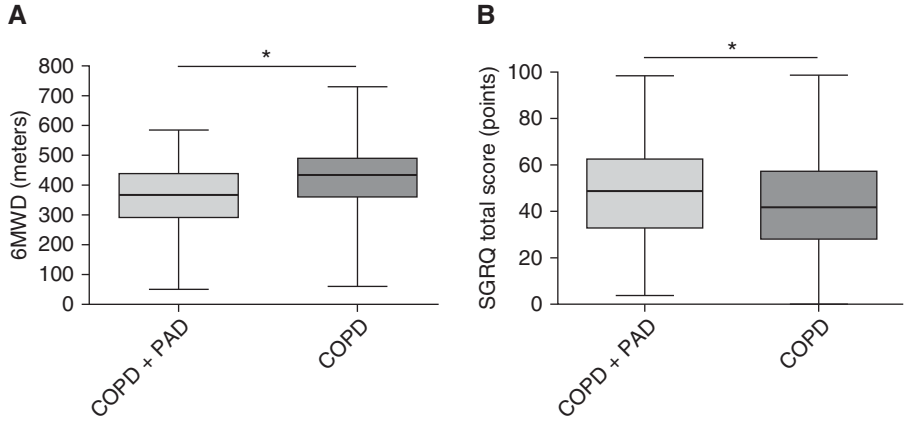

Figure 3. (*A*) The 6-minute-walk distance (6MWD) and (*B*) St. George's Respiratory Questionnaire (SGRQ) stratified by patients with and without peripheral artery disease (PAD). COPD = chronic obstructive pulmonary disease. *P ⩽ 0.05. Plots show mean values including upper and lower quartiles as well as minimum and maximum values.

Furthermore, we identified diffusion capacity to be independently associated with PAD in our cohort. The present study is the first showing a relationship between PAD and diffusion capacity for carbon monoxide in patients with COPD. Interestingly, our data are in line with a recent observation showing an association between coronary artery calcification and emphysema severity (40). Thus, both studies together suggest an association between emphysema and atherosclerotic processes. Previous findings indicated a higher prevalence of PAD in patients with more severe COPD (35, 41), which is supported by our univariate analyses. In a multivariate regression model, however, diffusion capacity remained an independent predictor for PAD only, whereas GOLD stages III and IV were no longer significant. However, smoking status was the strongest independent predictor of PAD, which is confirmed by a recent meta-analysis demonstrating that smoking status is the highest prevalent risk factor for cardiovascular disease in patients with COPD (38).

Functional Capacity

The 6MWD is assumed to evaluate the integrated responses of all systems involved during exercise, including peripheral circulation (21). Our study clearly demonstrates an association between objectively assessed PAD and functional capacity as quantified by 6MWD in COPD. Previous smaller studies provided conflicting results as to whether or not PAD is associated with 6MWD. Although a rather strong association has been shown by Castagna and colleagues (41) in 151 patients with COPD with GOLD stages II and III, Sun and colleagues (42) did not find a statistical significant difference in 6MWD between patients without PAD and those with PAD. Even after adjusting for several confounders, we found a rather large difference in 6MWD that clearly exceeded the MCID of 30 m compared with those without PAD. Interestingly, asymptomatic patients with PAD with an ABI less than 0.9 have previously been found to have a lower 6MWD than matched control subjects (43), which further strengthens the findings of our study.

Health Status

To the best of our knowledge, the current study is the first to evaluate the relationship

Table 3. Difference in Functional Capacity and Health Status between Patients with Chronic Obstructive Pulmonary Disease with and without Peripheral Artery Disease

Dependent Variable	Total Group (*N = 2,088*)	ABI ⩽ 0.9 (*n = 184*)	ABI > 0.9 (*n = 1,904*)	Unadjusted *P* Value	Adjusted Mean Difference (95% CI)	Adjusted *P* Value
6MWD, m	n = 2,028	n = 178	n = 1,850			
	417 (106)	356 (108)	422 (103)	**<0.001**	−40.9 (−54.5 to −27.4)	**<0.001**
SGRQ scores	n = 2,070	n = 183	n = 1,887			
SGRQ total score, points	43.3 (20.1)	49.7 (20.1)	42.7 (20.0)	**<0.001**	4.30 (1.45 to 7.14)	**0.003**
SGRQ symptom score, points	55.7 (21.3)	59.1 (20.4)	55.4 (21.3)	**0.025**	1.73 (−1.53 to 4.98)	0.298
SGRQ activity score, points	57.9 (25.8)	67.4 (22.8)	57.0 (25.9)	**<0.001**	6.33 (2.86 to 9.79)	**<0.001**
SGRQ impact score, points	30.5 (21.0)	36.1 (22.6)	29.9 (20.8)	**<0.001**	3.96 (0.88 to 7.03)	**0.012**
CAT total score, points	n = 2,075	n = 182	n = 1,893			
	18.1 (7.4)	19.6 (7.4)	17.9 (7.4)	**0.004**	1.13 (0.18 to 2.24)	**0.046**
EQ-5D-3L utility score, points	n = 2,075	n = 184	n = 1,891			
	0.82 (0.2)	0.79 (0.2)	0.82 (0.2)	**0.020**	−0.03 (−0.06 to 0.01)	0.102
EQ-5D VAS, points	n = 2,075	n = 184	n = 1,881			
	56.6 (19.6)	51.2 (19.0)	57.2 (19.6)	**<0.001**	−3.58 (−6.48 to −0.67)	**0.016**

Definition of abbreviations: 6MWD = 6-minute-walk distance; ABI = ankle–brachial index; CAT = Chronic Obstructive Pulmonary Disease Assessment Test; CI = confidence interval; D_{LCO} = diffusing capacity of the lung for carbon monoxide; EQ-5D = EuroQol-5 dimensions; EQ-5D-3L = EuroQol-5-dimensions instrument, 3 level version; GOLD = Global Initiative for Chronic Obstructive Lung Disease; SGRQ = St. George's Respiratory Questionnaire; VAS = visual analog scale. Values are expressed as mean (SD) unless otherwise indicated. Unadjusted *P* values are based on independent sample *t* test; adjusted *P* values are based on general linear model after correction for age, sex, height, weight, D_{LCO} % predicted, GOLD stage, smoking status, hypertension, myocardial infarction, and angina pectoris for 6MWD; and for age, sex, D_{LCO} % predicted, GOLD stage, smoking status, hypertension, myocardial infarction, and angina pectoris for health status. Bold values represent significant results.

between objectively assessed PAD and disease-specific as well as generic health status in patients with COPD. Because worse health status has been shown to be associated with diminished physical functioning (44, 45), it is not unexpected that the impairment in health status corresponded to the functional impairment in our cohort. Indeed, impairments in health status were most pronounced in the SGRQ activity domain. However, the difference in all other domains also clearly exceeded the minimum clinically relevant difference of 4 points. It seems to be a general finding that subjects with PAD report an impaired generic health status; this has been demonstrated using the Medical Outcomes Study 36-Item Short-Form Health Survey (46). Although differences in generic health status, as measured by EQ-5D-3L, were statistically significant in the current study, their clinical relevance might be disputable. Their lower sensitivity in the population studies is in line with reports that disease-specific questionnaires are more sensitive in patients with COPD (47).

Recently, the COMorbidities in Chronic Obstructive Lung Disease (COMCOLD) index has been developed, which includes PAD as one of the five most important comorbidities affecting patients' health status (48). The current study confirms these findings, as it demonstrates a clinically relevant association between PAD and disease-specific health status.

Limitations

Although the COSYCONET cohort study is a multicenter, longitudinal, prospective study that included a large number of patients throughout Germany, there are limitations that must be taken into account. First, the methodologies to detect PAD were not the same as those in SHIP and COSYCONET. However, this should only have a minor impact on the differences in prevalence of PAD, because the correlation between both measurement methods is acceptable in healthy subjects and patients with mild PAD with an ABI of 0.9 or less (10). Only in severe PAD with low ABI ranges is there an overestimation of the actual pressure by the oscillometric method, which does not affect the current prevalence comparison, as this is the cut-off level defining mild PAD (10). Second, stops and/or leg pain during the 6MWD have not been investigated, which could provide a better understanding of the differences found in 6MWD between patients with COPD with PAD and those without PAD. However, as the majority of patients had no previous diagnosis of PAD, it is likely that they were rather asymptomatic than symptomatic. Indeed, only 10 patients (0.5%) had an ABI of 0.6 or less, which represents the cut-off for severe, symptomatic PAD with intermittent claudication (49). Third, subjects with COPD and control subjects were not sampled from the same population (i.e., a nested case control study design), resulting in the potential risk of selection and confounding bias.

Conclusions

In a large cohort of patients with COPD, 8.8% had an ABI of 0.9 or less, indicating PAD. The prevalence of PAD was higher than the prevalence in matched control subjects from two epidemiological cohorts. Patients with COPD and PAD showed a clinically relevant impairment of functional capacity and disease-specific health status compared with those without PAD. Our study demonstrates that the presence of PAD is clearly associated with clinically relevant outcome measures that are established for monitoring patients with COPD. Therefore, clinicians should actively look for PAD in patients with COPD to identify patients at risk for vascular events, and to fully understand their impairments. Early diagnoses and treatment of PAD in patients with COPD may improve morbidity and mortality, which should be investigated in the future. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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