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Leg Atherosclerosis in Japanese COPD Patients: Prevalence of Undiagnosed Peripheral Artery Disease and Association between Leg Atherosclerosis and Clinical Indices

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ABSTRACT

Introduction: Several studies have suggested that decreased FEV_1 is associated with cardiovascular risk in COPD patients. **Objective:** To identify the prevalence of undiagnosed peripheral artery disease (PAD) and the relationship between leg atherosclerosis and clinical indices, which predict COPD mortality in Japanese COPD patients. **Methods:** We performed a cross-sectional study in 51 COPD patients and 51 age-matched, healthy control smokers. We measured ankle-brachial index (ABI) as a marker of atherosclerosis of the legs, pulmonary function, body mass index, modified Medical Research Council (MMRC) dyspnea scale, and smoking pack-years. We also calculated the ADO index (Age, Dyspnea, and Obstruction), an established predictor of mortality in COPD patients. Co-morbidities including diabetes mellitus, hypertension, and hypercholesterolemia were identified from blood laboratory tests and medical records. **Results:** Five subjects (9.8%) had an ABI < 0.9. ABI was significantly lower in the COPD patients than in the healthy control smokers ($p < 0.05$). The prevalence of PAD was marginally higher in COPD patients than in control smokers ($p = 0.09$), with the prevalence of ABI < 1.0 being significantly higher in COPD patients than in control smokers ($p = 0.04$). In the COPD patients, ABI showed significant correlations with age ($p = 0.006$), FEV_1 ($p = 0.004$), smoking pack-years ($p = 0.047$), MMRC dyspnea scale ($p = 0.0005$), SaO_2 ($p = 0.001$), and ADO index ($p < 0.001$). Multiple linear regression modeling showed the factors associated independently with ABI were age, FEV_1, smoking pack-years, MMRC dyspnea scale, and SaO_2. **Conclusion:** The risk of leg atherosclerosis in Japanese COPD patients is higher than in smokers without COPD. Leg atherosclerosis in COPD patients is associated with clinical indices that predict COPD mortality.

Keywords: COPD; Peripheral Artery Disease; Leg Atherosclerosis; Ankle-Brachial Index

1. Introduction

Tobacco smoking is the most important risk factor for both the development and progression of COPD. Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide [1]. Recently, COPD has been recognized as a systemic disease [2,3], and in particular, is associated with a markedly increased risk of cardiovascular disease [4], which accounts for approximately 25% to 40% of mortality in COPD patients [5,6]. OPD is characterized by chronic airflow limitation resulting from an excessive inflammatory response of the lungs to cigarette smoking [7], an established risk factor for cardiovascular disease. However, recent studies have also shown that COPD is associated with cardiovascular risk independent of classical risk factors [8-10]. Furthermore, several studies have demonstrated that atherosclerosis is associated with FEV_1 [11-14]. These findings indicate that the severity of COPD is associated with atherosclerosis.

Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis, and is a common disorder associated with a very high risk of myocardial infarction, ischemic stroke, and death [15]. The prognosis of patients with lower extremity PAD is characterized by an increased risk for cardiovascular ischemic events due to concomitant coronary artery disease and cerebrovascular disease [16,17]. There is evidence that these cardiovascular ischemic events are more frequent than ischemic limb events in cohorts of patients with lower extremity

PAD [18]. Lower extremity PAD should therefore be considered as a sign of potentially diffuse and significant arterial disease [15].

Several studies have reported that the rate of cardiovascular death in the smoking population in Japan is lower than in other developed countries [19,20]. However, there are no data comparing the prevalence of PAD in COPD patients and healthy smokers in the Japanese population, and only limited data on the relationship between leg atherosclerosis and clinical indices in COPD patients.

2. Method

2.1. Subjects Studied

Subjects with COPD with a smoking history and age-matched control smokers were recruited from an outpatient clinic at Shinko Hospital. The control smokers without COPD were recruited from individuals treated at our hospital for chronic bronchitis without lung function abnormalities, or for health status check-ups. Control smokers were ex-smokers or current smokers without lung function abnormalities. An age-matched (within 1 year) control smoker was selected randomly for each subject with COPD. Subjects with a history of respiratory infection within the previous 4 weeks, asthma, or active malignancy were not included in the study. Cardiovascular comorbidity was recorded carefully. Patients already diagnosed with PAD were excluded from the study.

Body mass index (BMI) was calculated as weight (in kilograms) divided by height squared (in meters). Hypertension was defined as either a systolic blood pressure ≧ 140 mmHg, diastolic blood pressure ≧ 90 mmHg, or self-reported use of antihypertensive medication. Diabetes mellitus was defined as either a fasting glucose level ≧ 126 mg/dl, a non-fasting glucose level ≧ 200 mg/dl, a self-reported physician diagnosis, or pharmacologic hypoglycemic treatment. Subjects with a low-density lipoprotein (LDL)-cholesterol level ≧ 140 mg/dl or using lipid-lowering drugs were considered to have hypercholesterolemia. The subjects also completed a medical history that included questions about their current smoking status and history.

Spirometry was performed on all subjects using a computed spirometer (CHESTAC-8800, CHEST M. I., Inc., Tokyo, Japan). The protocol for the lung function measurements conformed to the recommendations of the American Thoracic Society [21]. This study was approved by the Ethics Committee of Shinko Hospital, and informed consent was obtained from all subjects prior to enrollment.

2.2. Ankle-Brachial Index

The ABI is calculated as the ratio of ankle to arm systolic blood pressure and is used commonly in clinical practice to assess lower extremity PAD [15]. In all cases, the subjects rested in the supine position for 5 min before measurement of ABI. Using appropriately sized blood pressure cuffs, systolic blood pressure was measured in both brachial arteries and both leg arteries using an automated device. All measurements were performed by staff in a blinded manner. We used the measurement from the leg with the lower ABI in the analyses.

2.3. Clinical Evaluation

Patients completed the modified Medical Research Council dyspnea scale (MMRC) questionnaire [22]. The ADO index is calculated using age, MMRC, and FEV_1, and is a better predictor of mortality from COPD than the traditional BODE index [23]. The ADO score ranges from 0 to 10 points, with higher scores indicating higher mortality.

2.4. Statistical Analysis

JMP software (SAS Institute Inc., Cary, NC, USA) was used for the analyses. The results are presented as mean (SEM) or number (percentage). Differences between the COPD patients and control smokers were compared using unpaired Student's t-tests for continuous variables and χ^2-tests for categorical data. Spearman's rank test was used to examine correlations between the variables. Multivariate linear regression was performed using each parameter as a dependent variable in order to determine the independent predictors of ABI. Due to the strong association between age and SaO_2, these variables were included in separate models as candidate variables. *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. Subject Characteristics

The characteristics of the subjects are shown in **Table 1**. The mean age of the COPD subjects was 72.4 years. The prevalence of ABI < 0.9 was marginally higher in the COPD group than in the control group (9.8% vs 2.0%, $p = 0.092$). The prevalence of ABI < 1.0 was significantly higher in the COPD group than in the control group (19.6% vs 5.9%, $p = 0.037$). FEV_1, BMI, and ABI were significantly lower in the COPD subjects compared to the control smokers (all $p < 0.05$). Age, gender, smoking status and pack-year histories, and prevalence of comorbidities were similar between the two groups.

The association of ABI with cardiovascular risk factors and clinical indices

In the COPD patients, ABI correlated significantly with age ($r = -0.37$, $p = 0.006$), FEV_1 ($r = 0.28$, $p = 0.004$), smoking pack-years ($r = -0.28$, $p = 0.047$),

Table 1. Characteristics of the subjects.

	Control smoker (n = 51)	COPD (n = 51)	P-value
Age (yr)	72.1 (7.4)	72.4 (6.8)	0.76
Male gender, n (%)	45 (88.2)	44 (84.6)	0.56
Current smokers, n (%)	15 (30.0)	8 (15.7)	0.084
Pack-years	55.9 (31.6)	60.0(34.5)	0.66
FEV_1 (%)	95.4 (19.1)	47.2 (20.4)	<0.001
BMI (kg/m^2)	23.8 (3.4)	21.8 (3.5)	0.0042
ABI	1.13 (0.1)	1.07 (0.1)	0.0054
ABI < 0.9	1 (2.0)	5 (9.8)	0.092
ABI < 1.1	3 (5.9)	10 (19.6)	0.037
Comorbidity, n (%)			
Hypertension	14 (27.5)	19 (37.3)	0.29
Diabetes mellitus	8 (15.7)	4 (7.8)	0.22
Hypercholesterolemia	13 (25.5)	7 (13.7)	0.075
Ischemic heart disease	7 (13.7)	3 (5.9)	0.19

Values are expressed as mean (SD) unless stated otherwise.

MMRC dyspnea scale (r = −0.47, p = 0.0005), resting SaO_2 (r = 0.45, p = 0.001) (**Table 2**), and ADO index (r = −0.51, p < 0.001) (**Figure 1**). There were no associations between ABI and BMI, smoking status, prevalence of comorbidities, or history of ischemic heart disease (**Table 3**).

Multiple linear regression modeling, after adjustment for age, FEV_1, smoking pack-years, and MMRC dyspnea scale, showed that age (p = 0.0046), FEV_1 (p = 0.027), smoking pack-years (p = 0.0018), and MMRC dyspnea scale (p = 0.023) were independent factors associated significantly with ABI (**Table 4 (a)**). Adjustment for SaO_2, FEV_1, smoking pack-years, and MMRC dyspnea scale, showed that SaO_2 (p = 0.037), smoking pack-years (p = 0.037), and MMRC dyspnea scale (p = 0.013) were significant independent determinants of ABI (**Table 4 (b)**).

4. Discussion

In this study we showed that the prevalence of undiagnosed PAD was approximately 10% in Japanese COPD patients, a rate marginally higher than that of age-matched healthy control smokers. ABI in COPD patients was lower than in healthy smokers. Age, MMRC, FEV_1, smoking pack-years, and SaO_2 were associated with ABI in COPD patients. There was also a negative correlation between ABI and the ADO index, which predicts COPD mortality. To our knowledge, this is the first report on the prevalence of undiagnosed PAD in Japanese COPD patients and also the relationship between ABI and clinical-

Table 2. Association between continuous variables and ABI analyzed by spearman's rank test.

	r	p
Age	−0.37	0.006
FEV_1	0.28	0.004
BMI	0.079	0.58
Pack-years	−0.28	0.047
MMRC	−0.47	0.0005
SaO_2	0.45	0.001

Table 3. Mean difference in ABI between the dichotomous groups.

		p
Current smoking	0.053	0.18
Hypertension	0.0077	0.30
Hyperlipidemia	0.046	0.79
Diabetes mellitus	0.0027	0.96
Ischemic heart disease	0.074	0.25

Table 4. Multiple linear regression of ABI. (a) Adjusted for age, FEV1, pack-years, and MMRC; (b) Adjusted for SaO_2, FEV1, pack-years, and MMRC.

(a)

	OR	95% CI	p
Age	0.999	0.991 - 0.998	0.0046
FEV_1	1.001	1.000 - 1.003	0.027
Pack-years	0.998	0.998 - 0.999	0.0018
MMRC	0.977	0.958 - 0.996	0.023

(b)

	OR	95% CI	p
SaO_2	1.016	1.001 - 1.031	0.037
FEV_1	1.000	0.999 - 1.072	0.34
Pack-years	0.999	0.998 - 0.999	0.037
MMRC	0.973	0.953 - 0.993	0.013

indices associated with COPD mortality.

Approximately 10% of COPD patients in this study had an ABI < 0.9. There are only limited published data on the prevalence of lower extremity PAD in COPD patients. A high prevalence of lower extremity PAD in COPD patients was reported in a study from France, that showed 123 of 151 (81.4%) of patients with moderate-to-severe COPD had pathological ABI values (ABI < 0.9) [24]. On the basis of the findings of the present study it appears that the prevalence of lower extremity PAD in COPD patients in Japan may be lower than that in patients in Europe. One reason for this result may be that we excluded subjects who had already been diagnosed with PAD. Another reason may be that the prevalence of

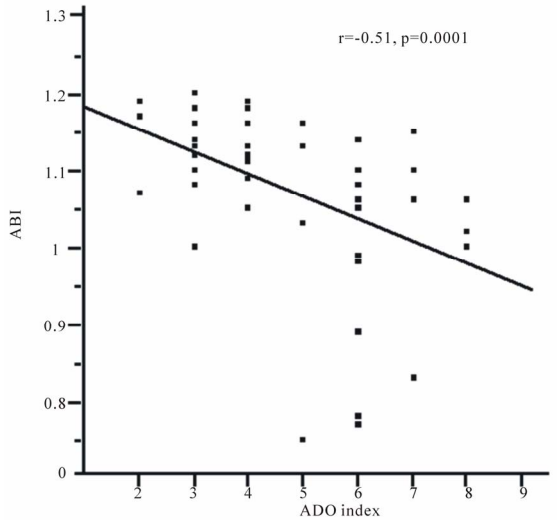

Figure 1. Association between ABI and ADO index. ABI showed a significant and negative correlation with ADO index ($r = -0.51$, $p = 0.0001$).

PAD is low in both COPD patients and the general population in Japan compared with other developed countries. Several studies have also reported that the rate of cardiovascular death in the smoking population and PAD patients is lower in Japan than in other developed countries [19,20,25,26]. However, in this study, the prevalence of PAD in COPD patients tended to be high, with the proportion of subjects with an ABI < 1.1 being significantly greater than in control subjects. Fowkes *et al.* demonstrated that subjects with an ABI 0.91 to 1.10 had higher mortality and cardiovascular event rates than those with a normal ABI [27]. Therefore, as in other countries, attention should be paid to the risk of cardiovascular diseases in Japanese COPD patients.

Recent studies have demonstrated that atherosclerosis is associated with FEV_1 [11-14]. In the Atherosclerosis Risk in Communities (ARIC) Study, decreased FEV_1 was associated with decreased ABI in smoking subjects even after adjustment for cardiovascular risk factors [12]. Iwamoto *et al.* [14], measured the carotid intima-media thickness and focal atheromatous plaque as indicators of subclinical atherosclerosis in patients with airflow limitation and control smokers. They showed that mean carotid intima-media thickness was greater in patients with an airflow limitation than in the controls. Furthermore, their data showed significant associations between thickened intima-media thickness and decreased FEV_1. Although the mechanism for these associations was unclear, it is possible hypoxia occurring in the later stages of COPD may have induced an abnormal inflammatory response, reflected by increased CRP [28] and oxidative stress [29]. In our study, resting SaO_2 showed a significant and positive correlation with ABI, and was an independent determinant of ABI. This finding indicates that hypoxia may contribute to atherosclerosis in COPD patients. Further studies are required to conclusively determine the mechanisms of these interactions.

We also showed that MMRC was associated with ABI. The severity of dyspnea has been shown to be a better predictor of mortality in COPD than airway obstruction [20]. COPD patients with the most severe dyspnea were shown to be more likely to die than those with only mild dyspnea [20]. A low ABI is a predictor of systemic atherosclerosis and risk of cardiovascular events [27]. Engstrom *et al.* reported that reduced FEV_1 was associated with an increased incidence of hospitalizations due to heart failure [30]. Therefore, not only poor lung function, but also impaired cardiac function may contribute to dyspnea in patients with a low ABI.

In this study, the presence of cardiac risk factors (hypertension, diabetes mellitus, and hypercholesterolemia) was not associated with ABI. One reason for this result may be that the prevalence of these diseases was low in COPD subjects in this study.

In the present study the ADO index correlated better with ABI than either age, FEV_1, or MMRC. The ADO index is a multidimensional index developed by Puhan *et al.* [23] that incorporates age, dyspnea, and airflow obstruction. The index predicts 3-year mortality from COPD more accurately than the BODE index, which is currently used to estimate a patient's risk of death from COPD. There is evidence that both these multidimensional indices predict survival better than FEV_1 alone [31]. Several studies have shown that airflow limitation is an independent risk factor for cardiovascular disease. However, there is no established threshold for the relationship between cardiovascular risk and FEV_1. In this study all patients with an ABI < 0.9 had an ADO index score of 5 points or greater. This result suggests that the ADO index has the ability to predict cardiovascular risk in COPD patients. A study in a large number of subjects is required to determine the cut-off point of the ADO index for screening cardiovascular disease in COPD patients.

Coronary and cerebrovascular diseases frequently coexist in PAD patients [15]. There is an approximately 2- to 4-fold excess of cardiovascular disease in patients with lower extremity PAD [16,17]. The prognosis of patients with lower extremity PAD is characterized by an increased risk for cardiovascular ischemic events due to concomitant coronary artery disease and cerebrovascular disease [16,17]. These cardiovascular ischemic events are more frequent than ischemic limb events in any cohort of patients with lower extremity PAD [18]. Lower extremity arterial disease should therefore also be viewed as a sign of potentially diffuse and significant arterial disease [15]. Measurement of ABI may be useful for identifying patients at high risk who may benefit from aggressive therapeutic intervention [32-35]. The guidelines of the Ame-

rican College of Cardiology (ACC) and American Heart Association (AHA) for the management of patients with PAD recommends that ABI should be considered as a routine test for all patients who are 49 years of age and younger with a history of diabetes and 1 other risk factor, those 50 to 69 years of age with a history of smoking or diabetes, and those aged 70 years or older [15]. In accordance with these guidelines the majority of COPD patients should have ABI measured.

There were some limitations in this study. The number of subjects was small and therefore a study on a larger number of subjects is needed to conclusively establish the prevalence of PAD in COPD subjects. Although some studies have reported an association between atherosclerosis and nocturnal hypoxia [36], the current study did not evaluate this relationship.

5. Conclusion

In this study we showed that the rate of atherosclerosis in COPD patients in Japan was lower than in similar patients in other developed countries. However, we showed the rate of atherosclerosis in COPD patients was higher than in healthy smokers, with this finding being consistent to data of other countries. Leg atherosclerosis was also shown to be associated with clinical indices related to COPD mortality. It is therefore important that more attention is paid to leg atherosclerosis in Japanese COPD patients.

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REFERENCES

[1] C. J. Murray and A. D. Lopez, "Global Mortality, Disability, and the Contribution of Risk Factors: Global Burden of Disease Study," *Lancet*, Vol. 349, No. 9063, 1997, pp. 1436-1442. doi:10.1016/S0140-6736(96)07495-8

[2] L. M. Fabbri, F. Luppi, B. Beghe, *et al*., "Complex Chronic Comorbidities of COPD," *European Respiratory Journal*, Vol. 31, No. 1, 2008, pp. 204-212. doi:10.1183/09031936.00114307

[3] J. D. Maclay, D. A. McAllister and W. Macnee, "Cardiovascular Risk in Chronic Obstructive Pulmonary Disease," *Respirology*, Vol. 12, No. 5, 2007, pp. 634-641. doi:10.1111/j.1440-1843.2007.01136.x

[4] D. D. Sin and S. F. Man, "Chronic Obstructive Pulmonary Disease as a Risk Factor for Cardiovascular Morbidity and Mortality," *Proceedings of the American Thoracic Society*, Vol. 2, No. 1, 2005, pp. 8-11. doi:10.1513/pats.200404-032MS

[5] P. M. Calverley, J. A. Anderson, B. Celli, *et al*., "Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease," *The New England Journal of Medicine*, Vol. 356, No. 8, 2007, pp. 775-789. doi:10.1056/NEJMoa063070

[6] R. A. Pauwels, C. G. Lofdahl, L. A. Laitinen, *et al*., "Long-Term Treatment with Inhaled Budesonide in Persons with Mild Chronic Obstructive Pulmonary Disease Who Continue Smoking," *The New England Journal of Medicine*, Vol. 340, No. 25, 1999, pp. 1948-1953. doi:10.1056/NEJM199906243402503

[7] W. MacNee, "Pathogenesis of Chronic Obstructive Pulmonary Disease," *Proceedings of the American Thoracic Society*, Vol. 2, No. 4, 2005, pp. 258-266. doi:10.1513/pats.200504-045SR

[8] H. J. Schunemann, J. Dorn, B. J. Grant, *et al*., "Pulmonary Function Is a Long-Term Predictor of Mortality in the General Population: 29-Year Follow-Up of the Buffalo Health Study," *Chest*, Vol. 118, No. 3, 2000, pp. 656-664. doi:10.1378/chest.118.3.656

[9] D. D. Sin, L. Wu and S. F. Man, "The Relationship Between Reduced Lung Function and Cardiovascular Mortality: A Population-Based Study and a Systematic Review of the Literature," *Chest*, Vol. 127, No. 6, 2005, pp. 1952-1959. doi:10.1378/chest.127.6.1952

[10] S. M. Curkendall, C. DeLuise, J. K. Jones, *et al*., "Cardiovascular Disease in Patients with Chronic Obstructive Pulmonary Disease, Saskatchewan Canada Cardiovascular Disease in COPD Patients," *Annals of Epidemiology*, Vol. 16, No. 1, 2006, pp. 63-70. doi:10.1016/j.annepidem.2005.04.008

[11] M. Zureik, A. Benetos, C. Neukirch, *et al*., "Reduced Pulmonary Function Is Associated with Central Arterial Stiffness in Men," *American Journal of Respiratory and Critical Care Medicine*, Vol. 164, No. 12, 2001, pp. 2181-2185.

[12] E. B. Schroeder, V. L. Welch, G. W. Evans, *et al*., "Impaired Lung Function and Subclinical Atherosclerosis. The ARIC Study," *Atherosclerosis*, Vol. 180, No. 2, 2005, pp. 367-373. doi:10.1016/j.atherosclerosis.2004.12.012

[13] D. A. McAllister, J. D. Maclay, N. L. Mills, *et al*., "Arterial Stiffness Is Independently Associated with Emphysema Severity in Patients with Chronic Obstructive Pulmonary Disease," *American Journal of Respiratory and Critical Care Medicine*, Vol. 176, No. 12, 2007, pp. 1208-1214. doi:10.1164/rccm.200707-1080OC

[14] H. Iwamoto, A. Yokoyama, Y. Kitahara, *et al*., "Airflow Limitation in Smokers Is Associated with Subclinical Atherosclerosis," *American Journal of Respiratory and Critical Care Medicine*, Vol. 179, No. 1, 2009, pp. 35-40. doi:10.1164/rccm.200804-560OC

[15] A. T. Hirsch, Z. J. Haskal, N. R. Hertzer, *et al*., "ACC/AHA 2005 Practice Guidelines for the Management of Patients with Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic): A Collaborative Report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interven-

tional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop," *Circulation*, Vol. 113, No. 11, 2006, pp. e463-e654.

[16] M. H. Criqui, J. O. Denenberg, R. D. Langer, *et al*., "The Epidemiology of Peripheral Arterial Disease: Importance of Identifying the Population at Risk," *Vascular Medicine*, Vol. 2, No. 3, 1997, pp. 221-226.

[17] J. Ness, W. S. Aronow, "Prevalence of Coexistence of Coronary Artery Disease, Ischemic Stroke, and Peripheral Arterial Disease in Older Persons, Mean Age 80 Years, in an Academic Hospital-Based Geriatrics Practice," *Journal of the American Geriatrics Society*, Vol. 47, No. 10, 1999, pp. 1255-1256.

[18] J. I. Weitz, J. Byrne, G. P. Clagett, *et al*., "Diagnosis and Treatment of Chronic Arterial Insufficiency of the Lower Extremities: A Critical Review," *Circulation*, Vol. 94, No. 11, 1996, pp. 3026-3049. doi:10.1161/01.CIR.94.11.3026

[19] D. R. Jacobs Jr., H. Adachi, I. Mulder, *et al*., "Cigarette Smoking and Mortality Risk: Twenty-Five-Year Follow-Up of the Seven Countries Study," *The Archives of Internal Medicine*, Vol. 159, No. 7, 1999, pp. 733-740. doi:10.1001/archinte.159.7.733

[20] K. Nishimura, T. Izumi, M. Tsukino, *et al*., "Dyspnea Is a Better Predictor of 5-Year Survival than Airway Obstruction in Patients with COPD," *Chest*, Vol. 121, No. 5, 2002, pp. 1434-1440. doi:10.1378/chest.121.5.1434

[21] American Thoracic Society, "Standardization of Spirometry," *American Journal of Respiratory and Critical Care Medicine*, Vol. 152, No. 3, 1995, pp. 1107-1136.

[22] D. A. Mahler, C. K. Wells, Evaluation of Clinical Methods for Rating Dyspnea," *Chest*, Vol. 93, No. 3, 1988, pp. 580-586. doi:10.1378/chest.93.3.580

[23] M. A. Puhan, J. Garcia-Aymerich, M. Frey, *et al*., "Expansion of the Prognostic Assessment of Patients with Chronic Obstructive Pulmonary Disease: The Updated BODE Index and the ADO Index," *Lancet*, Vol. 374, No. 9691, 2009, pp. 704-711. doi:10.1016/S0140-6736(09)61301-5

[24] O. Castagna, A. Boussuges, E. Nussbaum, *et al*., "Peripheral Arterial Disease: An Underestimated Aetiology of Exercise Intolerance in Chronic Obstructive Pulmonary Disease Patients," *European Journal of Cardiovascular Prevention & Rehabilitation*, Vol. 15, No. 3, 2008, pp. 270-277. doi:10.1097/HJR.0b013e3282f009a9

[25] T. Fujiwara, S. Saitoh, *et al*., "Prevalence of Asymptomatic Arteriosclerosis Obliterans and Its Relationship with Risk Factors in Inhabitants of Rural Communities in Japan: Tanno-Sobetsu study," *Atherosclerosis*, Vol. 177, No. 1, 2004, pp. 83-88.

[26] H. Ohnishi, Y. Sawayama, *et al*., "Risk Factors for and the Prevalence of Peripheral Arterial Disease and Its Relationship to Carotid Atherosclerosis: The Kyushu and Okinawa Population Study (KOPS)," *Journal of Atherosclerosis and Thrombosis*, Vol. 30, Vol. 17, 2010, pp. 751-758.

[27] F. G. Fowkes, G. D. Murray, I. Butcher, *et al*., "Ankle Brachial Index Combined with Framingham Risk Score to Predict Cardiovascular Events and Mortality: A Meta-Analysis," *Journal of the American Medical Association*, Vol. 300, No. 2, 2008, pp. 197-208. doi:10.1001/jama.300.2.197

[28] G. Hartmann, M. Tschop, R. Fischer, *et al*., "High Altitude Increases Circulating Interleukin-6, Interleukin-1 Receptor Antagonist and C-Reactive Protein," *Cytokine*, Vol. 12, No. 3, 2000, pp. 246-252. doi:10.1006/cyto.1999.0533

[29] V. Savransky, A. Nanayakkara, J. Li, *et al*., "Chronic Intermittent Hypoxia Induces Atherosclerosis," *American Journal of Respiratory and Critical Care Medicine*, Vol. 175, No. 12, 2007, pp. 1290-1297. doi:10.1164/rccm.200612-1771OC

[30] G. Engstrom, O. Melander, B. Hedblad, 'Population-Based Study of Lung Function and Incidence of Heart Failure Hospitalisations," *Thorax*, Vol. 65, No. 7, 2010, pp. 633-638. doi:10.1136/thx.2010.135392

[31] B. R. Celli, C. G. Cote, J. M. Marin, *et al*., "The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease," *The New England Journal of Medicine*, Vol. 350, No. 10, 2004, pp. 1005-1012. doi:10.1056/NEJMoa021322

[32] M. McKenna, S. Wolfson and L. Kuller, "The Ratio of Ankle and Arm Arterial Pressure as an Independent Predictor of Mortality," *Atherosclerosis*, Vol. 87, No. 2, 1991, pp. 119-128. doi:10.1016/0021-9150(91)90014-T

[33] M. T. Vogt, M. McKenna, S. J. Anderson, *et al*., "The Relationship between Ankle-Arm Index and Mortality in Older Men and Women," *Journal of the American Geriatrics Society*, Vol. 41, No. 5, 1993, pp. 523-530.

[34] G. C. Leng, F. G. Fowkes, A. J. Lee, *et al*., "Use of Ankle Brachial Pressure Index to Predict Cardiovascular Events and Death: A Cohort Study," *British Medical Journal*, Vol. 313, No. 7070, 1996, pp. 1440-1444. doi:10.1136/bmj.313.7070.1440

[35] H. E. Resnick, R. S. Lindsay, M. M. McDermott, *et al*., "Relationship of High and Low Ankle Brachial Index to All-Cause and Cardiovascular Disease Mortality: The Strong Heart Study," *Circulation*, Vol. 109, No. 6, 2004, pp. 733-739. doi:10.1161/01.CIR.0000112642.63927.54

[36] R. Schulz, Seeger, *et al*., "Changes in Extracranial Arteries in Obstructive Sleep Apnoea," *European Respiratory Journal*, Vol. 25, No. 1, 2005, pp. 69-74.

Abbreviations

COPD: Chronic Obstructive Pulmonary Disease
FEV_1: Forced Expiratory Volume in one second
PAD: Peripheral Artery Disease
ABI: Ankle-Brachial Index
BMI: Body Mass Index
MMRC: Modified Medical Research Council
SaO_2: Arterial Oxygen Saturation
Ease of Use (*Heading* 2)

