CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ARTERIAL STIFFNESS

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ABSTRACT

Comorbidities are common in chronic obstructive pulmonary disease (COPD). Cardiovascular comorbidity is a leading cause of morbidity and mortality in COPD patients. Low lung function is a risk factor for increased arterial stiffness, a condition that is common in COPD patients, independent of conventional cardiovascular risk factors. Arterial stiffness is an independent risk factor both for all-cause and for cardiovascular mortality, and carotid–femoral pulse wave velocity is the gold standard for the assessment of arterial stiffness. Various mechanisms proposed in the development of arterial stiffness include systemic inflammation, ageing, advanced glycation end products, renin–angiotensin–aldosterone system, increased elastolysis, and vitamin D deficiency. Early detection of arterial stiffness in COPD patients is warranted to detect cardiovascular comorbidity at the subclinical stage, which would help to prevent overt vascular events in the future. We need well-designed studies to see the impact of therapy that targets increased arterial stiffness on future cardiovascular events in COPD. This review discusses the epidemiology, diagnosis, and therapy of increased arterial stiffness in COPD patients.

Keywords: Chronic obstructive pulmonary disease (COPD), arterial stiffness, pulse wave velocity (PWV), augmentation index (AIx).

INTRODUCTION

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) as "a common preventable and treatable disease, characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients."[1] COPD has a substantial impact in terms of morbidity, mortality, and economic loss.[2,3] Comorbidities may be present in the early stages of COPD[4] and are associated with a higher risk of exacerbations, hospitalisations, poor health status, and mortality.[5] Cardiovascular disease (CVD) is a major comorbidity and a significant contributor to morbidity and mortality in COPD patients. COPD patients have a 2 to 3-fold higher risk of developing CVD compared with the normal population[6,7] and the increased risk is independent of conventional cardiovascular risk factors such as smoking, ageing, and hypercholesterolaemia. In a large systematic review and meta-analysis, Chen et al.[8] showed that COPD is a risk factor for major CVD, and cardiovascular risk factors such as smoking, diabetes, and hypertension.

CVD is the leading cause of hospitalisation in patients with mild-to-moderate COPD.[9] About 12–50% of total deaths in COPD patients are attributed to this cardiovascular cause.[10] COPD patients have a 30% higher risk of sudden cardiac death, and the risk is higher in the frequent exacerbator phenotype.[11] Shared risk factors such as smoking, indoor air pollution, and ageing can explain the high prevalence of CVD in COPD patients. Other mechanisms include systemic inflammation, oxidative stress, physical inactivity, autonomic dysfunction, hypoxia, hypercapnia, and drug effects. Vascular dysfunction is an important mechanism that can explain the COPD–CVD link. COPD patients develop various vascular changes

such as carotid intima media thickness, endothelial dysfunction, and arterial stiffness. Arterial stiffness is a marker of early atherosclerosis[12] and is an independent predictor of CVD and cardiovascular events.[13] In a systematic review and meta-analysis of 17 longitudinal studies, Vlachopoulos et al.[14] reported that aortic stiffness is an independent risk factor both for all-cause and cardiovascular mortality. Every 1 metre (m)/second (s) increase in aortic pulse wave velocity (PWV) increases all-cause and cardiovascular mortality by 15%. Arterial stiffness is increased significantly in COPD patients compared to control subjects,[15] and early detection of arterial stiffness in COPD may help in adopting necessary preventive measures to avert future major overt vascular events.[16]

Disadvantages of Arterial Stiffness

The arterial pulse wave is generated by ventricular contraction. It has two main components: a forward-propagating wave and a reflected wave. Systolic ventricular contraction ejects the stroke volume into the vascular system, thereby generating the pulsatile forward-propagating wave. Resistance in the peripheral vascular system creates the reflected wave.[17] The reflected waves return during the diastolic phase in healthy persons and contribute to coronary perfusion. The pulsatile blood flow pattern may cause damage to high-flow and low-resistance cerebral and renal vascular systems.

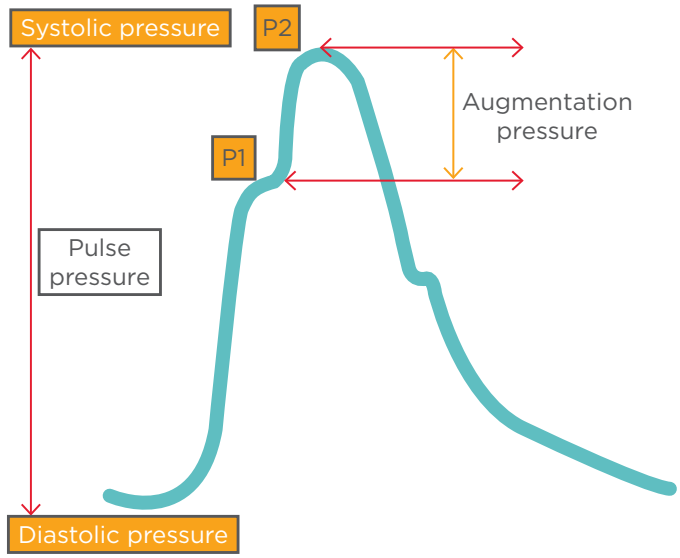

Figure 1: Augmentation pressure and pulse pressure.
Point P1 is the forward wave and point P2 is the reflecting wave. The difference between the reflected and forward wave is the augmentation pressure.

However, the elastin fibre-rich aorta dampens the pulsatile flow and prevents pressure-induced damage to cerebral and renal vascular systems. A stiffened aorta would fail to prevent the pulsatile flow-mediated target organ damage.[18] John et al.[19] have shown significantly increased microvascular renal damage in COPD patients related to increased arterial stiffness. Arterial stiffness also causes the earlier return of the reflected waves, during the systolic phase, rather than during diastole. It causes augmentation of systolic blood pressure (BP), development of left ventricular hypertrophy, and reduced coronary perfusion. This phenomenon of augmenting the systolic pressure by the reflected waves is measured by the augmentation index (AIx). Left ventricular hypertrophy manifested in electrocardiography is associated with a 3 to 15-fold increase in the risk of cardiovascular events.[20]

MEASUREMENT OF ARTERIAL STIFFNESS

There are several techniques to measure arterial stiffness, but in clinical practice PWV is the most commonly used non-invasive method.[13] PWV determines the speed at which the pulse wave travels over an arterial segment. It is measured as the ratio of the distance (m) to time (s) between two pressure waves recorded transcutaneously at two arterial sites. PWV can be measured in any arterial segment, but aortic stiffness measured as the carotid–femoral (cf)-PWV is considered the gold standard measurement of arterial stiffness,[13] as cf-PWV is a strong independent predictor of future adverse cardiovascular events.[14] cf-PWV is the ratio of the distance (m) and transit time (s) between the common carotid and femoral artery sites. The distance is measured by a tape from the sternal notch to the right carotid and the right femoral artery. The expert consensus document on the measurement of aortic stiffness recommends that 80% of the carotid–femoral distance should be used as the most accurate distance estimate of true aortic length.[21] The transit time measures the time delay between the proximal and distal pulse waves, and is most commonly measured by the foot-to-foot method. The foot of the pulse wave is defined as the point of minimal diastolic pressure or as the beginning of the steep rise in the systolic pressure. PWV depends on the elasticity of the arterial wall and its dimension.[22] Mean PWV in a healthy, normotensive person is 6.1±1.4 m/s.[23] Aortic PWV >10 m/s is considered a marker of target organ damage.[24]

AIx measures the augmentation of BP during the systolic phase by the reflected waves. Figure 1 shows the aortic pulse waveform derived from the radial artery. The AIx is the difference between the first and second systolic peaks as a percentage of pulse pressure. AIx is calculated by the following equation: AIx (%) = (ΔP/PP)×100. ΔP is the pressure difference between the peak systolic pressure (P2) and the first systolic peak that indicates the beginning upstroke of the reflected pressure wave (P1). In the equation, PP stands for pulse pressure. The gold standard and most commonly used technique to measure AIx is applanation tonometry.[25] It does not directly measure the central artery pressure waveform; instead, the aortic pressure waveform is derived from the radial artery pressure waveform.[26]

ARTERIAL STIFFNESS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD patients have consistently shown increased arterial stiffness across studies compared with ex-smokers without airway obstruction and with non-smoking healthy controls.[15]

In a cross-sectional study, Sabit et al.[27] measured arterial stiffness in 75 clinically stable COPD patients and 42 healthy current or ex-smoking participants. All participants were free of CVD. Arterial stiffness was measured by the SphygmoCor® CPV System (AtCor Medical, Sydney, Australia), and both the aortic PWV and the AIx were measured. Presence of osteoporosis was evaluated by measuring bone mineral density by a dual-energy X-ray absorptiometry scan. Both PWV and AIx were significantly higher in COPD patients than in age-matched controls. Increased aortic PWV was related to increased severity of airflow obstruction, systemic inflammation, and the presence of osteoporosis. Arterial stiffness was increased even with a mild degree of airway obstruction, indicating its early occurrence in the natural history of COPD.

In a prospective case-control study, Mills et al.[28] evaluated arterial stiffness in 102 patients with COPD and 103 healthy controls matched for age and smoking status. Using applanation tonometry (SphygmoCor CPV system), they measured the augmentation pressure and AIx of the radial artery at the wrist and derived the aortic pulse pressure waveform via a mathematical transfer function. COPD patients had elevated augmentation pressures (17±1 mmHg versus 14±1 mmHg, p=0.015) and reduced time-to-wave reflection (131±1 versus 137±2 m/s, p=0.005) compared with controls. Serum C-reactive protein concentrations were also significantly higher in COPD patients compared with controls and may explain the higher frequency of arterial stiffness in COPD patients.

Arterial stiffness is higher in severe COPD compared to mild-to-moderate COPD. A prospective cross-sectional study from Turkey by Cinarka et al.[29] assessed cf-PWV in 62 stable COPD patients and 22 healthy controls by using the SphygmoCor CPV system. The mean cf-PWV was significantly elevated in patients with COPD compared to the controls (10.95±3.74 m/s versus 7.32±1.88 m/s, p=0.003). Severe COPD patients had higher cf-PWV values compared to patients with the mild-to-moderate disease. They found airflow limitation measured by forced expiratory volume in 1 second (FEV_1) as the only independent predictor of cf-PWV.

Patel et al.[30] evaluated the aortic PWV and cardiac biomarkers in 98 COPD patients in a stable condition. Fifty-five of the patients were assessed in both stable state and exacerbation. Arterial stiffness was related to exacerbation frequency, and frequent exacerbators had greater mean aortic PWV than infrequent exacerbators (11.4±2.1 versus 10.3±2.0 m/s, p=0.025). Compared with the stable state, arterial stiffness increased acutely during episodes of exacerbation by 1.2 m/s, and the rise was higher in exacerbation caused by infection. Vlachopoulos et al.[14] performed a meta-analysis of 17 longitudinal studies involving 15,877 subjects that measured arterial stiffness by aortic PWV and showed that a 1 m/s increase in aortic PWV resulted in an age–sex and risk factor adjusted increase in total cardiovascular event, cardiovascular mortality, and all-cause mortality, of 14%, 15%, and 15%, respectively.

Bolton et al.[31] studied the relationship between aortic calcification and arterial stiffness in stable COPD patients and found a significant association between aortic PWV and calcification in the aorta. Age was the independent predictor of both processes. Bhatt et al.[32] evaluated arterial stiffness in 153 patients with moderate-to-severe COPD and found that age, higher systolic BP, and greater thoracic aortic calcification are independent predictors of elevated aortic PWV in multivariate analyses. Elastolysis in the aorta is the stimulus for calcium deposition. Qin et al.[33] demonstrated that inhibiting matrix metalloproteinases (MMPs), which are markers of elastolysis, reduced vascular calcium

deposition. Arterial stiffness is also increased in bronchiectasis, which is common in COPD.[34] In patients with acute exacerbation of COPD, Labonté et al.[35] found increased blood levels of club cell protein (CC16) and RelB levels, both of which have an inverse relation with arterial stiffness.

MECHANISM OF ELEVATED ARTERIAL STIFFNESS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The following factors have been incriminated in the development of arterial stiffness in COPD. They include some common risk factors, such smoking, physical inactivity, and ageing. Others include airway obstruction, systemic inflammation, oxidative stress, advanced glycation end products (AGEs), and renin–angiotensin–aldosterone system (RAAS).

Airway Obstruction and Emphysema

Airway obstruction is an independent risk factor for arterial stiffness. The Caerphilly population-based Prospective Study[36] found an inverse relationship between forced vital capacity (FVC) and FEV_1 with cf-PWV in men. They also observed that lung function assessments in mid-life rather than in later-life were stronger predictors of arterial stiffness and future CVD. This association was independent of smoking status, early life events, and inflammatory and metabolic factors. A 500 mL reduction in FEV_1 and FVC in mid-life resulted in PWV increases of 0.52 m/s and 0.42 m/s, respectively.

In a cross-sectional study involving 194 men, aged 30–70 years, who were free of coronary heart diseases, Zureik et al.[37] found a significant negative relationship between lung function parameters like FEV_1, FVC, and cf-PWV, suggesting that both obstructive and restrictive lung disorders are associated with increased arterial stiffness. This relationship is also independent of traditional cardiovascular risk factors such as smoking, hypercholesterolaemia, and hypertension. In an age and height-adjusted analysis, a decrease of 195.2±50.1 mL in FEV_1 and 190.4±55 mL in FVC increased the cf-PWV by 2.5 m/s.

McAllister et al.[16] demonstrated that arterial stiffness measured in 157 stable COPD patients (aortic PWV determined by the SphygmoCor CVD System) was related to emphysema severity (measured by quantitative thoracic computed tomography). This association was independent of smoking, age, sex, airflow limitation, systemic inflammation, dyslipidaemia, and hypoxaemia. One possible explanation for low lung function and arterial stiffness could be an alteration of elastolytic activity in both the alveoli and the vasculature. Elastolysis in COPD can occur in both the pulmonary and systemic levels. Maclay et al.[38] demonstrated increased skin elastin degradation in COPD patients compared to age and smoking-matched controls. The cutaneous level of MMP-9 messenger RNA was also increased in COPD patients. Upregulated skin elastolysis was related to the severity of emphysema and arterial stiffness. COPD patients probably develop increased elastin degradation in elastin-rich large conduit arteries such as the aorta that may explain increased arterial stiffness in COPD patients. The rise in elastolysis may be environmental or due to genetics. Studies have proven the common role of MMPs, an elastolytic enzyme, in both conditions. Serum levels of both MMP-9 and MMP-12 were found to be increased in both COPD and arteriosclerosis.[16] Furthermore, a polymorphism in MMP-9 increased the risk of both arterial stiffness and emphysema.[39,40]

Advanced Glycation End Products

AGEs are a heterogeneous group of substances formed irreversibly by non-enzymatic glycation and the oxidation of proteins, lipids, and nucleic acids.[41]

The classic Maillard reaction generates AGEs via several intermediate stages. Initially, Schiff base and Amadori products are formed via reversible reactions, and the final oxidation process leads to AGE formation.[42] An increased AGE level is seen in oxidative and inflammatory conditions like hyperglycaemia, renal failure, and COPD.[43,44] AGEs have been found to play a role in the pathogenesis of both COPD and arterial stiffness. AGEs, via the receptor for AGEs (RAGEs), may cause oxidative and inflammatory stress in tissues.[45,46] Wu et al.[44] have shown increased expression of both AGEs and RAGEs in COPD lung tissues compared to controls. The RAGE–AGEs axis can amplify and propagate cigarette smoking-induced airway inflammation in COPD patients.[47] AGEs can cause arterial stiffness by forming irreversible cross-links with proteins such as collagen and elastin. These proteins become structurally and functionally altered after glycation. AGEs may also affect endothelial cell synthesis of nitric oxide (NO). Rojas et al.[48] have shown significant reduction in endothelial NO synthase expression in bovine aortic endothelial cells after exposure to

albumin-derived AGEs. Kemeny et al.[49] similarly showed reduced NO release by cells of glycated collagen. NO reduces vascular oxidative stress and inflammation, the two key factors for atherosclerosis formation. Urban et al.[50] have demonstrated a link between reduced levels of soluble RAGE and endothelial dysfunction during acute COPD exacerbation. The soluble RAGE normally functions as a decoy receptor for AGEs, thereby limiting inflammation.

Renin–Angiotensin–Aldosterone System

The RAAS is activated in COPD and its role has been found in the causation of COPD and its extra-pulmonary manifestations.[51,52] Angiotensin II is a potent vasoconstrictor and vasoproliferator substance. Vasoproliferator action is mediated by the binding of angiotensin II to the angiotensin Type 1 (AT1) receptor present in vascular tissues.[53,54] Hypercholesterolaemia and diabetes are two important causes of increased expression of the AT1 receptor in vascular tissue,[55,56] and both the conditions are seen in COPD in high frequency.[57] Rats with fructose-induced hyperinsulinaemic conditions showed increased vascular AT1 receptor expression.[58] The increase in RAAS or AT1 may lead to structural changes of the vasculature, leading to altered vasoreactivity and arterial stiffness.

Vitamin D Deficiency

Vitamin D deficiency is common in COPD patients and is more prevalent in severe COPD. Janssens et al.[59] found vitamin D deficiency in 60% and 77% of patients with GOLD Stage 3 and 4 COPD, respectively, compared with 31% of smokers with normal lung function. Vitamin D deficiency has also been incriminated in causing increased arterial stiffness and endothelial dysfunction independent of traditional risk factors. In a community-based asymptomatic population study, Al Mheid et al.[60] observed that low vitamin D levels are independently associated with increased PWV, AIx, and impaired flow-mediated dilatation after adjustments of confounders such as age, sex, race, BMI, total cholesterol, low-density lipoprotein, triglycerides, C-reactive protein, and medication use. There are various mechanisms by which vitamin D deficiency can cause endothelial dysfunction. Vitamin D normally inhibits the deleterious effects of AGEs on endothelial cells.[61] Vitamin D deficiency by activating RAAS may produce vasoproliferative actions.[60]

Ageing

Both COPD and its systemic manifestations are related to an accelerated ageing process. Oxidative stress has a role in this ageing process. Boyer et al.[62] studied the telomere shortening and systemic manifestations in 100 COPD patients, and smoking and non-smoking controls without COPD. COPD patients showed higher PWV, reduced bone mineral density and appendicular skeletal muscle mass index, and increased telomere length shortening; features not seen in control smokers. Therefore, systemic manifestations in COPD are mainly due to COPD itself.

Systemic Inflammation and Oxidative Stress

Systemic inflammation is common in COPD patients and has been identified as one of the mechanisms associated with a higher risk of CVD in COPD patients. In a systematic review and a meta-analysis, Gan et al.[63] reported the presence of systemic inflammation in COPD patients, which may explain the high prevalence of comorbidities in COPD. Sin and Mann[64] have shown that in patients with moderate-to-severe airflow obstruction, low-grade systemic inflammation explained the increased risk of cardiac injury in COPD. However, the association between systemic inflammation and arterial stiffness varies in literature. Several studies have shown a positive association between systemic inflammation and arterial stiffness.[16,27] A study conducted with healthy volunteers using *Salmonella* typhi vaccination as a model of acute systemic inflammation showed endothelial dysfunction and an increase in arterial stiffness.[65,66] Further studies have shown no link between the two.[67-69] It can be explained by the varying methodologies in these studies. Mills et al.[28] found no significant differences in C-reactive protein levels in COPD patients with and without cardiovascular comorbidities.

Moreover, not all COPD patients show systemic inflammation.[70] Systemic inflammation causes arterial stiffness by altering the extracellular matrix of the vasculature.[71] It causes the degradation of elastic fibres by elastolysis and their replacement by collagen.[72] An important biomarker of elastin degradation is the plasma desmosine (pDES) level. Rabinovich et al.[73] have shown that pDES levels were significantly higher in COPD patients with CVD and correlated with arterial stiffness ($p<0.05$). However, no correlation was seen with emphysema or emphysema progression indicating that pDES is

primarily a marker of vascular elastin degradation. Systemic inflammation by altering NO production may also lead to functional arterial stiffness development.[74] Hypoxaemia is another mechanism in COPD that has been linked to arterial stiffness.[29] It may be mediated by a hypoxaemia-induced rise in systemic inflammation.[75]

Altered Redox Balance in Chronic Obstructive Pulmonary Disease

Ives et al.[76] showed that compared to age and sex-matched controls, COPD patients developed altered redox balance characterised by lower antioxidant effects and higher oxidative stress. Altered redox balance has been linked with increased PWV in COPD as an antioxidant cocktail (vitamin C, vitamin E, α-lipoic acid), and was associated with significant improvements in PWV in patients with COPD. Oxidative stress alters arterial stiffness by impacting on the endothelial NO pathway.[77]

TREATMENT OF AORTIC STIFFNESS

Comprehensive management of COPD should also include assessment and management of comorbidities. However, current COPD guidelines are not focussed on this issue. Arterial stiffness can be modifiable. Endurance exercise has been shown to improve arterial stiffness in the healthy person.[78,79] It does so in COPD patients also. A case-controlled study by Vivodtzev et al.[67] evaluated the impact of exercise in 17 stable COPD patients. Endurance exercise lasting 4 weeks resulted in a significant reduction in carotid-radial PWV in COPD patients. The improvement in arterial stiffness occurred proportionally to changes in exercise capacity. The mechanisms of improvement include a reduction in BP and blood glucose. Exercise training lowers BP by reducing basal sympathetic activity and restoring baroreflex sensitivity.[80] Another mechanism may be an exercise-induced reduction in oxidative stress and subsequent arterial stiffness.[23] Gale et al.[68] conducted a prospective cohort study which further supported the role of exercise as a modifier of arterial stiffness. A multidisciplinary pulmonary rehabilitation programme resulted in improvement in several cardiovascular risk factors in COPD patients: aortic PWV, BP, and cholesterol.

Dransfield et al.[81] conducted a multicentre, randomised, double-blind, placebo-controlled study, which evaluated the effects of fluticasone propionate/salmeterol (FSC; 250/50 µg) twice daily on aortic PWV in COPD patients. Reduction in PWV is maximum in patients with highest baseline arterial stiffness and is only seen in those patients who continued the therapy throughout the study period. Sabit et al.[82] similarly evaluated the effects of FSC (500/50 µg) in patients with moderate-to-severe COPD and found significant improvement in arterial stiffness after 8 weeks of treatment. The exact mechanism by which inhaled corticosteroid improves arterial stiffness is not known. It may be mediated by its impact on systemic inflammation,[83] or neurohumoral activation.[84] Statins having an anti-inflammatory effect would be an attractive option in COPD with CVD. In a double-blind, randomised trial, John et al.[85] evaluated the effects of simvastatin 20 mg once daily for 6 weeks on aortic stiffness, and systemic and airway inflammation in patients with COPD. Simvastatin improved aortic PWV only in the subgroup with a higher baseline PWV (>10 m/s). Beta blockers with vasodilatory effect, for example nebivolol, have the potential to reduce arterial stiffness by increasing NO activity.[86] Nebivolol also demonstrates anti-inflammatory effects which are also responsible for an improvement in vascular function.[87] Although beta blockers appear to be safe in COPD, their role in terms of reduction in arterial stiffness and the subsequent impact on cardiovascular comorbidity needs to be studied in prospective randomised, controlled trials.[88]

CONCLUSION

CVD occurs frequently and is a major cause of morbidity and mortality in COPD patients. Arterial stiffness is an independent predictor of adverse cardiovascular events and all-cause mortality. Arterial stiffness is increased in patients with COPD and there are several potential mechanisms by which COPD can influence the development of arterial stiffness. Early detection of arterial stiffness is important for future prevention of overt CVD.

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