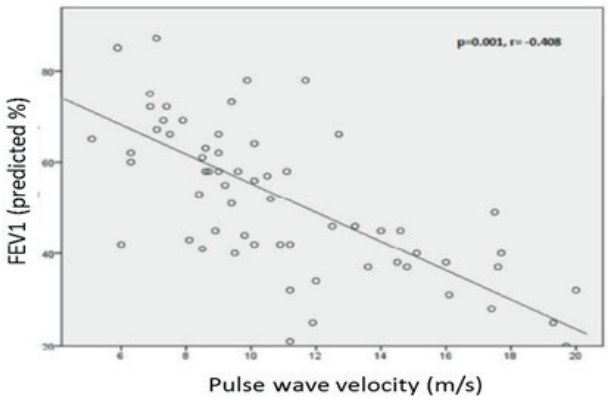
Aortic Stiffness and Chronic Obstructive Pulmonary Disease

The effects of COPD, now recognised as a chronic inflammatory disease, are not limited to the respiratory system. In fact, the primary cause of morbidity and mortality in mild-to-moderate cases of COPD is cardiovascular disease. Even in COPD patients with greatly impaired lung function, the majority of deaths are from cardiovascular disease[1,2]. Thus, the evaluation and management of COPD, along with the assessment of the cardiovascular effects of new drugs, should include measurements of cardiovascular disease risk factors.

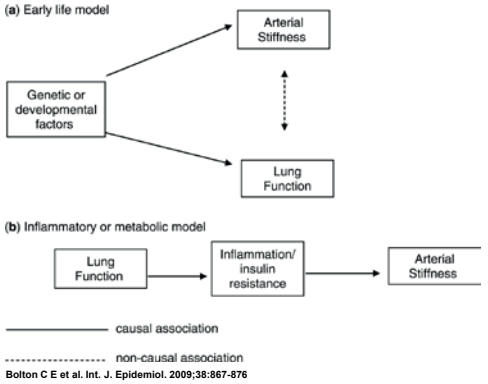
Arterial stiffness, especially stiffness in the large elastic arteries such as the aorta, is now widely recognised as an important factor in the development and progression of heart disease. Over the past several years, the measurement of aortic stiffness has been shown to be an independent and significant predictor of future events in a wide range of cardiovascular diseases. The most widely used measurement is the carotid-femoral pulse wave velocity (cfPWV), an easily performed, standardised measurement with established reference values[3,4]. A recent meta-analysis of over 16,000 subjects showed that hazard ratios for an elevated cfPWV ranged from 1.33 to 1.52 for all-cause mortality, CVD, CHF, and stroke[5]. Hazard ratios when grouped according to age showed that cfPWV is higher in younger (<51 years old) subjects than in the oldest subjects (>70 years old) – 1.75 vs. 1.24, respectively. In addition, net reclassification rates, indicating that subjects would be reclassified into higher or lower risk categories when cfPWV was included in risk classification, ranged from 18.6 % for CHD and 22.4 % for stroke.

Aortic stiffness has been gaining recognition as an important parameter in two aspects of COPD. It is an independent predictor of cardiovascular disease, as described above, but has also recently been shown to be associated with decreased lung function[6]. In a study by Cinarka *et al*. only FEV_1 was found to be an independent predictor of cfPWV. These results are shown in the figure below.



Two possible mechanisms have been suggested to explain the association between aortic stiffness, COPD, and cardiovascular disease[7]. One is that genetic and lifestyle factors lead to parallel adverse changes in aortic stiffness and lung function. A second mechanism is that inflammatory and metabolic (insulin) changes that occur in COPD directly lead to increases in aortic stiffness.

Conceptual models examining the association between lung function and arterial stiffness: (a) early life and socioeconomic model, (b) inflammatory or metabolic model.



Bolton C E et al. Int. J. Epidemiol. 2009;38:867-876

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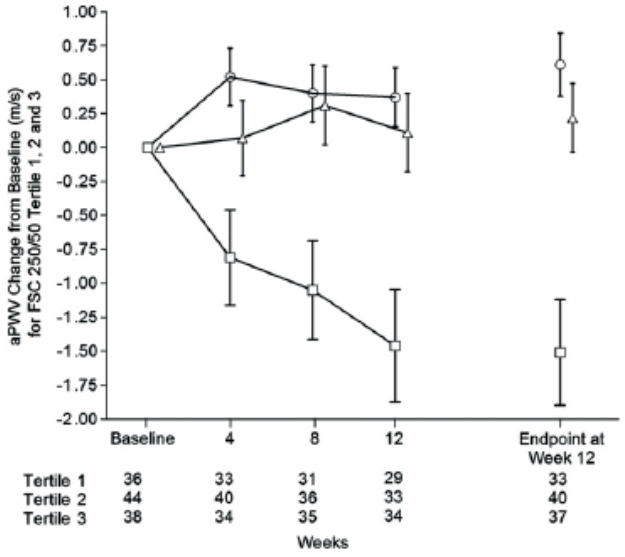
In either case, an increase in aortic stiffness, i.e., cfPWV, has been shown to be associated with decreased lung function and an increased severity of COPD.

The carotid to femoral pulse wave velocity is typically measured by recording the pressure waveform non-invasively at the carotid and femoral arteries, either simultaneously or with a reference time marker such as an EKG. From the two waveforms, the time interval between the arrival of the waveforms at each site (Δt) is determined and the distance between the sites (Δx) is used to compute the cfPWV[4]:

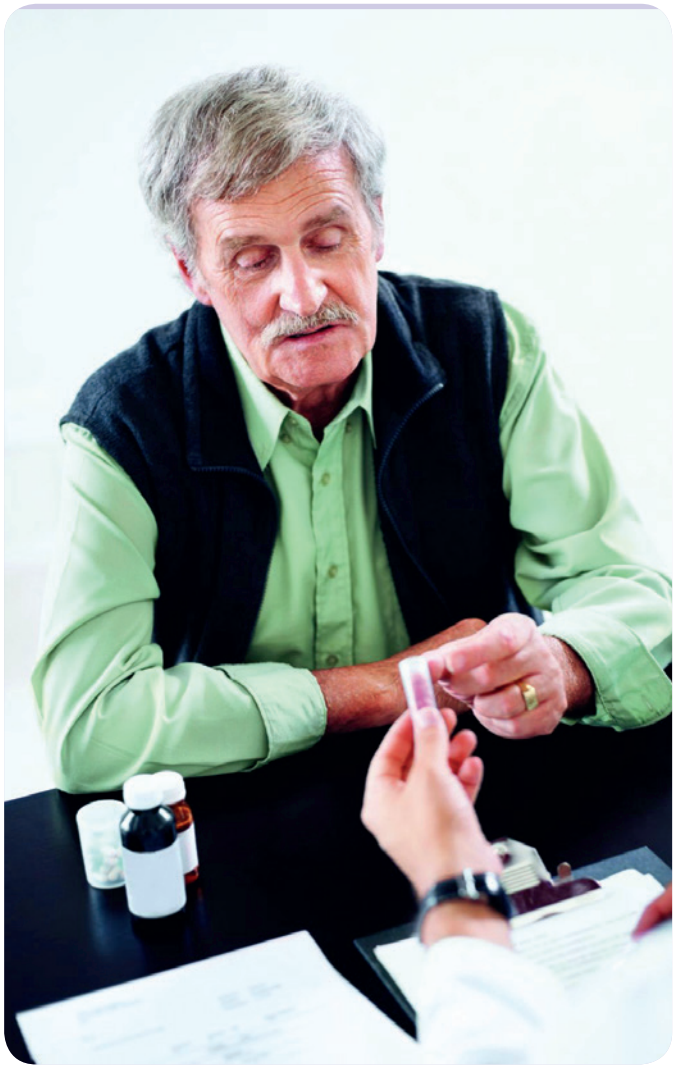
$$cfPWV = \Delta x / \Delta t.$$

A number of systems are now available that allow rapid and easy measurement of cfPWV. The reproducibility of many of these systems (e.g., the SphygmoCor XCEL from AtCor Medical and the Complior from Alam Medical, the two most widely used systems) has been shown to be quite good. Mean differences of intra-observer values are less than 0.2m/s and for inter-observer values are less than 0.5m/s for both systems.

Recently, cfPWV has been used to assess vascular changes and associated CVD risk differences in COPD drugs. A study by Dransfield *et al*. looked at the effect of the combination of a corticosteroid and long-acting beta antagonist on aortic stiffness.



The figure shows the change in cfPWV from baseline in the FSC group. Values are means ± SE. Open circles denote Tertile 1. Open triangles denote Tertile 2. Open squares denote Tertile 3. Tertile 1 was defined by having baseline cfPWV measures ≤ 8.7m/s; Tertile 2: 8.7m/s < cfPWV ≤ 10.9m/s; Tertile 3: cfPWV >10.9m/s. At the 12 week endpoint, Tertile 3 cfPWV was significantly lower than placebo (p=0.05).



Other studies have confirmed that drug combinations can lower cfPWV, especially in patients with elevated cfPWV values at the start of treatment.

In summary, COPD is now often referred to as a cardiovascular disease since cardiovascular diseases are the prime contributor to morbidity and mortality, especially in people under 50 years old. Because of the significance of cardiovascular disease in COPD, patient risk assessment should include risk factors for CVD. Aortic stiffness has been shown to be an independent and highly significant predictor of CVD events, and when added to traditional risk scores, significantly improves those scores. In addition, aortic stiffness measures can be altered by drugs currently being evaluated for treatment of COPD so that these measures are useful in evaluating cardiovascular risk effects of these treatments. Aortic stiffness measures, specifically the carotid-femoral pulse wave velocity, can be useful both in the assessment of COPD patients and the assessment of new drugs to treat COPD.

References

1. *Huiart et al., Cardiovascular morbidity and mortality in COPD, Chest, 2005; 128: 2640–2646*
2. *Sin, Is COPD really a cardiovascular disease?, Chest, 2009; 136: 329-330*
3. *Boutouyrie et al., Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values,' Eur Hrt J, 2010; 31: 2338–2350*
4. *Van Bortel et al., Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity, J Hypertens, 2012; 30: 445-448*
5. *McIniery et al., Prognostic value of carotid-femoral pulse wave velocity for cardiovascular events, presented at Artery 12, Vienna, Austria, Oct, 2012*
6. *Cinarka et al., Arterial stiffness measured by carotid femoral pulse wave velocity is associated with disease severity in chronic obstructive pulmonary disease, Resp Care, 2013; in press – online: July 2, 2013*
7. *Bolton et al., Lung function in mid-life compared with later life is a stronger predictor of arterial stiffness in men, International J Epidemiology, 2009; 38: 867–876*
8. *Dransfield et al., The effect of fluticasone propionate/salmeterol on arterial stiffness in patients with COPD, Resp Med, 2011;105:1322-1330*

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