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EDITORIAL

# Arterial Stiffness, Exercise Capacity and Cardiovascular Risk

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Large artery stiffening is widely believed to be the primary driver of isolated systolic hypertension and is recognised as a major cardiovascular risk factor [1]. Since arterial stiffness modulates the speed at which blood pressure waves propagate along arteries, and since the greatest loss of arterial compliance with ageing occurs in the aorta, the most popular surrogate index of arterial stiffness is carotid-femoral pulse wave velocity (cf-PWV) [1–4]. This is estimated by measuring the time delay between carotid and femoral arterial pulses and the length between these sites. The potential clinical utility of cf-PWV is supported by numerous studies. For example, Vallée et al. [5] found that, after correction for age, sex and blood pressure, cf-PWV had high specificity as a predictor of coronary heart disease and provided added value to carotid plaque and dyslipidaemia in a clinical decision tree. More broadly, in a large meta-analysis of patient and population cohorts, Ben-Shlomo et al. [3] showed that each standard deviation increase in ln(cf-PWV) was independently associated with a 30% increased risk of cardiovascular disease events and mortality.

Arterial stiffness is influenced by a range of factors (Figure 1). With normal ageing, cf-PWV increases by around 0.2–0.4 m/s per decade in early adulthood, accelerating to 1.2–2.4 m/s per decade in 80 year olds; thus, cf-PWV more than doubles from approximately 5 to 13 m/s over the life span [2,6]. The concept of 'vascular ageing' arises from findings that the rise in cf-PWV with chronological age may be accelerated by other factors. In particular, high blood pressure is associated with higher cf-PWV independent of age as well as steeper cf-PWV trajectories [2,4,7]; in terms of causation, this is a two-way interaction forming a vicious cycle, where elevated cf-PWV increases pulse pressure, while high blood pressure increases cf-PWV due to the non-linearity of the pressure-diameter relationship as well as accelerating degradation of elastic wall components through increased mechanical stresses. While a range of data suggest that elevated cf-PWV precedes the rise in blood pressure [1,8], data from the Young Finns Study showed not only that children with elevated blood pressure tend to have higher cf-PWV as adults, but that resolution of elevated childhood blood pressure led to a decreased risk of high cf-PWV in adulthood [9].

Other factors associated with higher cf-PWV include male sex, smoking, dyslipidaemia and diabetes; however, with the exception of diabetes, these may be mediated by blood pressure and age [4,7]. By contrast, a number of studies have reported an independent link between elevated arterial stiffness and inflammation, as evidenced by associations with the proinflammatory cytokine leptin or the inflammatory marker C-reactive protein [10–14]. Inflammatory effects on endothelial function and other cell signalling may act to raise arterial stiffness, for example through increased rate of elastin degradation, reduced nitric oxide bioavailability, increased endothelin-1 activity and increased collagen synthesis [15]. Data reported by Zanoli et al. [10] suggest these alterations may, in some cases, be reversible with resolution of the inflammatory condition.

Whereas ageing, hypertension and inflammation all promote arterial stiffening, regular aerobic exercise has been shown to attenuate or even reverse stiffening [16,17]. A number of mechanisms contribute to this phenomenon, including mechanical, metabolic, neurohormonal and anti-inflammatory processes which will not be comprehensively reviewed here. A key benefit of exercise is its blood pressure-reducing effects [18], which occur via increased nitric oxide bioavailability, decreased plasma endothelin I and norepinephrine concentrations [19], in combination with increased angiogenesis and lower vascular resistance. Reducing blood pressure in turn releases tension on the arterial wall, leading to reduced stiffness. In regards to inflammation, exercise has been shown to have a therapeutic effect through the

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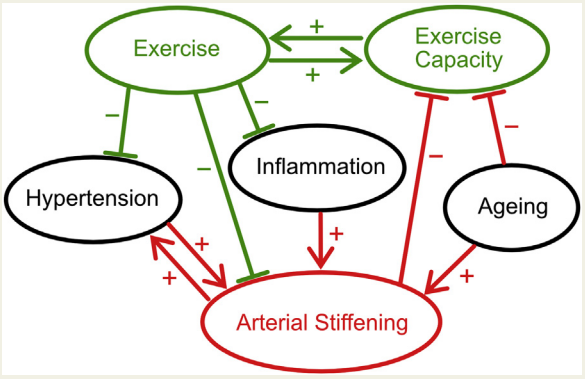


**Figure 1** Interactions between exercise and arterial stiffening. Green and red lines indicate beneficial and deleterious physiological effects respectively.

up-regulation of super-oxide dismutase [20], anti-inflammatory cytokines [21] and the down regulation of NAD(P)H [20]. Exercise and arterial stiffness are thought to have a dose dependent relationship, i.e. increased exercise intensity leads to greater reductions in cf-PWV, while the benefit of commencing exercise also appears to be greater in those with higher baseline cf-PWV [16].

A potential barrier to achieving the benefits of exercise is that elevated arterial stiffness is associated with reduced exercise capacity [22]. While this likely arises in part from low levels of exercise causing both lower fitness and elevated arterial stiffening (via the pathways mentioned above), it is also thought that high arterial stiffness limits exercise capacity via two haemodynamic effects. First, it raises systolic blood pressure and hence ventricular workload and metabolic demands of the myocardium. Second, it reduces the reservoir capacity (or 'windkessel function') of the large arteries, so that less blood is retained in the stiff large arteries during systole for discharge to tissues during diastole. The result is a faster diastolic decay of aortic blood pressure and a reduced coronary perfusion pressure. This imbalance between systolic workload and diastolic perfusion is often quantified via the subendocardial viability ratio, that is, the ratio of the systolic pressure time integral (SPTI, a surrogate of myocardial oxygen demand) and the diastolic pressure time integral (DPTI, a surrogate of myocardial oxygen supply). This ratio decreases with increasing cf-PWV [23] (Figure 2) and negatively correlates with coronary flow reserve in patients without significant stenoses [24]. A role of cf-PWV in limiting coronary flow reserve was also demonstrated by Kingwell et al. [25] who showed that cf-PWV was a major determinant of myocardial ischaemic threshold during exercise in patients with coronary heart disease.

To date, limited data exist on the link between exercise capacity and cf-PWV in patients with coronary artery disease. In this issue of *Heart, Lung and Circulation*, Alves et al. [26] report that higher cf-PWV was associated with reduced exercise capacity in patients enrolled in a cardiac rehabilitation program following acute myocardial infarction. $VO_2$peak was approximately 25% lower in patients in the highest vs lowest cf-PWV tertile, and there was a relatively strong negative correlation (Pearsons r= -0.5) between $VO_2$peak and cf-PWV. Not surprisingly, patients aged <60 years with 'young arteries' (cf-PWV<10 m/s) had significantly higher exercise

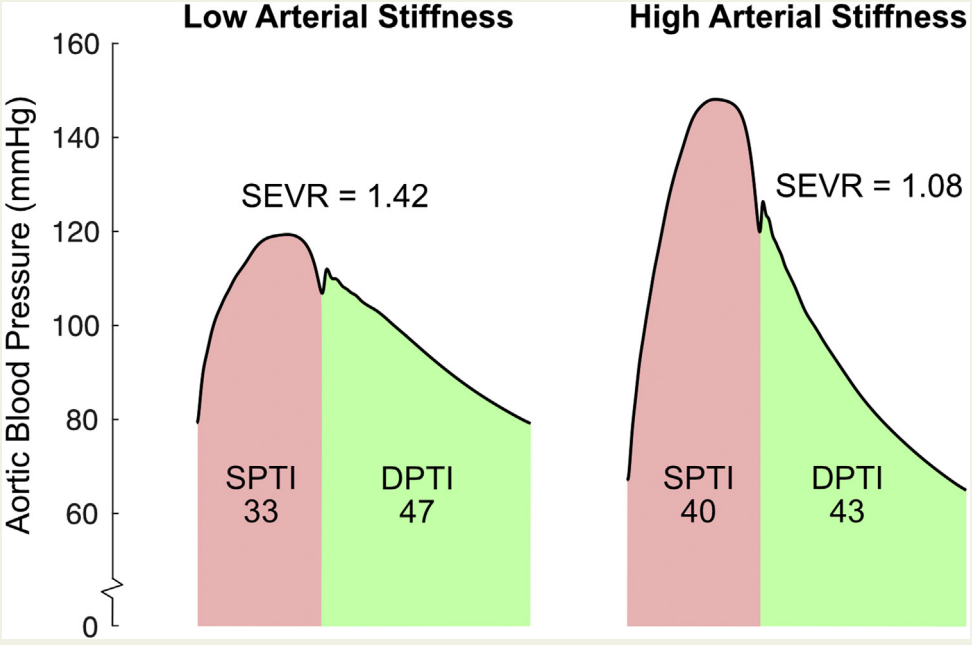


**Figure 2** Arterial stiffening causes widening of pulse pressure, increased systolic pressure time integral (SPTI) that reflects myocardial oxygen demand, and decreased diastolic pressure time integral (DPTI) that reflects myocardial oxygen supply. The balance of supply and demand therefore decreases, quantified via the subendocardial viability ratio (SEVR = DPTI/SPTI), leading to lower exercise capacity and ischaemic threshold.

capacity than those aged ≥60 years who had 'old arteries' (cf-PWV≥10 m/s). On the other hand, no difference was detected between younger patients with 'old arteries' and the chronologically older subgroups. Although this may imply that greater arterial age in the younger patients underlies a reduced exercise capacity, the study was not powered for this question and therefore the results cannot be interpreted as confirming no difference between these subgroups. Nevertheless, a lower $VO_2$peak in the third cf-PWV tertile of the overall cohort remained significant after adjustment for age (and other risk factors), suggestive of a vascular ageing effect independent of chronological age.

The findings of Alves et al. [26] adds to a wealth of literature supporting the importance of regular aerobic exercise throughout life in maintaining compliant arteries, limiting harmful increases in blood pressure and inflammation, and reducing cardiovascular risk. As such, exercise training interventions may be a powerful approach for reducing long term risk in children and young people with a predisposition to higher cf-PWV, elevated blood pressure and/or lower exercise capacity (e.g. those with a history of prematurity, intra-uterine growth restriction, repaired aortic coarctation, overweight/obesity [27–31]), as well as in at-risk adult sub-populations (e.g. obesity, metabolic syndrome, type 2 diabetes and heart disease [32]).

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