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COMMENTARY

Novel therapeutic strategies for reducing arterial stiffness

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Despite over half a century of intensive research, cardiovascular disease remains the leading cause of death worldwide. A number of risk factors for cardiovascular disease have been identified, such as hypertension, serum cholesterol and smoking. Accumulating evidence also suggests that arterial stiffness is an additional important and independent predictor of cardiovascular risk. Indeed, data from several large, prospective studies demonstrate that aortic pulse-wave velocity, a robust index of large artery stiffness, predicts both cardiovascular and all-cause mortality in a number of patient populations (Blacher *et al*., 1999; Laurent *et al*., 2001; Meaume *et al*., 2001; Cruickshank *et al*., 2002; Sutton-Tyrrell *et al*., 2005). However, arterial stiffness may not be just a marker of cardiovascular risk, but may also play a pathophysiological role in driving the development of cardiovascular disease.

Normally, the large arteries serve primarily to buffer the cyclical changes in blood pressure resulting from intermittent cardiac ejection. However, as the arteries stiffen, this buffering capacity is reduced, leading to a number of adverse haemodynamic consequences. One such consequence is a rise in aortic pulse pressure, which is itself strongly correlated with carotid intima–media thickness (Boutouyrie *et al*., 1999) and independently predicts outcome in patients with end-stage renal failure (Safar *et al*., 2002) and cardiovascular events in patients with hypertension (Williams, 2005). Increased aortic pulse pressure in turn causes increased levels of cyclical stress on the arterial wall, a rise in left ventricular afterload and a decrease in myocardial perfusion, thus substantially increasing the risk of cardiovascular events.

A further consequence of arterial stiffening is the development of isolated systolic hypertension (ISH), which is the most common form of hypertension in older individuals, affecting $\sim$50% of those aged over 60 years (Franklin *et al*., 2001). Although traditionally viewed as a benign condition and simply part of the natural ageing process, ISH is now regarded as the most common clinical manifestation of arterial stiffening and is associated with considerable increased risk of coronary heart disease, stroke and heart failure (Nielsen *et al*., 1995; Staessen *et al*., 2000). Moreover, ISH is frequently resistant to treatment and many patients never reach target pressures (Franklin *et al*., 2001). A potential explanation for the lack of efficacy in treating ISH is that current regimes are based around traditional anti-hypertensive agents such as thiazide diuretics and calcium channel blockers, which act mainly by reducing the mean arterial (vessel distending) blood pressure. Although this approach can reduce arterial stiffness, it does so passively, rather than *via* a *direct* effect on the large arteries themselves. Moreover, a side effect of lowering mean arterial pressure is a reduction in diastolic pressure which, paradoxically, may have adverse clinical consequences because coronary artery perfusion occurs predominantly in diastole. The importance of lowering arterial stiffness itself is further emphasised by previous findings in patients with end-stage renal failure, where a reduction in mean pressure alone, without any concomitant reduction in arterial stiffness, was associated with an adverse outcome (Guerin *et al*., 2001). Therefore, drugs that can selectively target the large arteries may provide a more successful therapeutic approach with which to reduce arterial stiffness directly.

Arterial stiffness is determined by a number of factors, including structural elements within the arterial wall, vascular smooth muscle tone and the mean arterial pressure. Although age exerts the most marked influence on arterial stiffening (McEniery *et al*., 2005), certain conditions such as hypertension and diabetes also exacerbate this process (Cockcroft *et al*., 2000). The age-related changes in arterial stiffness are, to a large extent, thought to be structurally driven. Indeed, a number of changes in the arterial wall have been described with age, including alterations in the ratio of elastin, collagen and other matrix proteins. More recently, a role for advanced glycation end products (AGEs) in the development of arterial stiffening has been suggested. These are a heterogeneous group of protein and lipids to which sugar residues are covalently bound, and accumulate slowly on long-lived matrix proteins such as elastin and collagen (Brownlee *et al*., 1988). A number of previous studies have demonstrated that the resultant cross-bridge formation between AGEs and structural proteins such as collagen leads to increased arterial and myocardial stiffness in animal models of ageing (Cantini *et al*., 2001), diabetes (Brownlee *et al*., 1988) and hypertension (Ooshima & Midorikawa, 1977; Mizutani *et al*., 2002) and in humans (Kass *et al*., 2001). Therefore, therapies which either prevent or retard the development of AGEs present an interesting and potentially valuable target for novel therapies to reduce arterial stiffening.

In this issue, Chan *et al*. (2006) report that aminoguanidine, which inhibits AGEs and protein crosslinking, prevents the detrimental changes in cardiac and vascular structure and function, associated with development of hypertension. Using the DOCA-salt hypertensive rat model, which is characterised by increased collagen crosslinking, treatment with aminoguanidine reduced systolic blood pressure markedly in the DOCA-salt rats and, to a lesser degree in controls, and attenuated the

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development of left and right ventricular hypertrophy and the decrease in ascending aortic arch diameter. Moreover, aminoguanidine prevented the increase in diastolic stiffness that was observed in control rats and improved vascular reactivity to noradrenaline, acetylcholine and sodium nitroprusside. This study extends upon previous findings showing that aminoguanidine is effective in preventing cardiac hypertrophy and arterial stiffening in animal models of ageing and diabetes (Li *et al*., 1996; Corman *et al*., 1998) by demonstrating an improvement in cardiac and vascular structural and functional indices in a hypertensive model. However, it is unlikely that the current data can be extended to humans, as the reported side effects associated with chronic aminoguanidine administration in humans include vasculitis and abnormalities in liver function (Freedman *et al*., 1999). However, newer, less toxic agents (pyridoxamine, ALT-946, OPB-9195) are currently undergoing clinical testing and may prove to be a safer alternative to aminoguanidine.

Although the current study highlights a potentially important strategy by which to prevent or retard the development of arterial stiffening, this approach is unlikely to be useful in older individuals or patients with ISH, because it is likely that in such individuals, arterial stiffening is already well established. An alternative therapeutic strategy for these individuals might lie in a new class of anti-AGE agents, including the thiazolium derivative ALT-711, which breaks down established AGE crosslinks. Data in animals demonstrate that this compound reduces arterial and myocardial stiffness (Wolffenbuttel *et al*., 1998; Asif *et al*., 2000; Vaitkevicius *et al*., 2001). Moreover, in humans, ALT-711 improves arterial compliance in older individuals with stiffened arteries (Kass *et al*., 2001). Therefore, therapies that break established crosslinks, rather than preventing their formation, might prove to be more useful in patients in whom arterial stiffening is already advanced. Nevertheless, agents that inhibit the development of AGEs present an intriguing opportunity to prevent the process of arterial stiffening. Other targets remain to be identified, but such strategies might also substantially reduce the incidence of ISH and the considerable excess cardiovascular risk associated with this condition.

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