"...the individual has now passed forty years, perhaps fifty years of age, his lungs begin to degenerate, he has a cough in the winter time, but by his pulse you will know him."

F. A. Mohamed, 1879 [1]

Introduction

Ageing is associated with little change in the pattern of left ventricular ejection [2]. However, stiffening of the arteries, an inevitable consequence of the ageing process in humans, produces characteristic changes in the arterial pulse [2]. The nineteenth century physician Akbar Mohamed recognized that the character of the arterial pulse changes with age as well as in diseases associated with premature vascular ageing [1, 3]. Although his approach was empirical and intuitive, recent research and the application of new methods has since confirmed that the pulse can, indeed, be used to assess arterial stiffening associated with ageing and cardiovascular disease, which may have an important influence on prognosis. Moreover, an understanding of the pulse waveform has led to a better appreciation of the interaction between ageing and arterial stiffness, which may lead to novel therapeutic approaches to reduce the mortality from cardiovascular disease.

Large arteries are not simply passive conduits but also serve to buffer the large changes in pressure resulting from intermittent ventricular ejection, thereby maintaining a head of pressure during diastole which enhances coronary and peripheral blood flow. In order to achieve this, the large arteries need to be compliant, accommodating the large volume of blood ejected from the ventricle, storing a proportion of the stroke volume during systole and releasing it during diastole. Stiffening of the large arteries occurs with age and leads to increased systolic and pulse pressure [4–6]. Systolic pressure is an important risk factor for cardiovascular morbidity and mortality [7] and this risk increases with advancing age [8].

Pulse wave analysis

Arterial pressure is generally measured at the brachial artery using sphygmomanometry. However, this only provides information on the extremes of pressure (systolic and diastolic pressure). Although correlation with aortic pressures may be reasonable for diastolic measurement, systolic aortic pressure is overestimated in youth and relatively underestimated as the arteries stiffen. The speed at which the forward pressure wave, generated at the aortic root at the beginning of systole, propagates throughout the vascular tree (the pulse wave velocity; PWV) is largely determined by the stiffness of the aorta and large peripheral arteries [9]. Stiffness is in part determined by distending pressure and in part by other functional and structural properties of the blood vessels. The stiffer the arteries, the faster the PWV [10]. Whereas the reflected wave returns to the aortic root in diastole in younger subjects, serving to augment diastolic pressure and enhance coronary blood flow, in older subjects and others with stiffer arteries a combination of enhanced reflection of the forward pressure wave at the periphery, coupled with earlier return of the wave to the central arteries because of increased PWV, leads to a late systolic peak in arterial pressure increasing cardiac load (Figure 1). These effects account for the discrepancy between brachial and aortic pressure. High central pressures, discussed in detail later, have a number of clinically important consequences. It has been assumed that age-related changes in arterial
stiffness are determined primarily by structural irreversible modifications (arteriosclerosis) in the large arteries. If increased stiffness of these arteries were due in part to functional changes, most likely mediated though the endothelium, then these abnormalities might be reversible with treatment.

To study age-related changes in pulse contour requires a simple, accurate and non-invasive method for measuring pulse pressure [11]. Such methodology is now available, pioneered by O'Rourke and colleagues in Sydney and based on the principle of applanation tonometry [12]. This involves flattening the curved surface of a pressure-containing structure (such as the radial artery) using a pencil-shaped probe incorporating a micromanometer at its tip. When this is achieved, the circumferential stresses in the vessel wall are balanced and the pressure and waveform are accurately recorded [11]. The arterial pressure wave changes as it travels from the aorta to the periphery and so the radial wave will be different from that recorded in the aorta [13]. However, it is now possible to synthesize the central aortic pressure wave from that recorded with tonometry in the periphery by applying a reverse transfer function. The 'derived' wave is almost identical to that recorded invasively [14, 15]. Using pulse wave analysis, arterial stiffness has been shown to increase with age [2]—confirming previous studies using other techniques [16]—and other cardiovascular risk factors which influence vascular 'ageing', such as diabetes [17] and

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**Figure 1.** The arterial pressure wave and pulse wave analysis: schematic representation of arterial pressure waves from a ascending aorta and b brachial artery. The upper part depicts waveforms in a young subject, the lower in a middle-aged one. With increasing age the reflected wave returns earlier. In the aorta this has the effect of increasing systolic pressure and cardiac work, but in the periphery it does not, since it remains in diastole. Augmentation is defined as $\Delta P/PP$, where $PP$ is the pulse pressure and $\Delta P$ the difference in height between the first and second systolic peaks. This is normally expressed as a percentage.
hypertension [18]. This has been attributed to the structural changes which characterize arteriosclerosis [19].

The endothelium

It is unlikely that physical structure alone determines the pulse pressure waveform, because it can be altered substantially by a number of therapeutic interventions [20–22]. The endothelial cells lining the large and resistance arteries do not function simply as a diffusion barrier between the circulating blood and the underlying vascular smooth muscle. They actively generate a variety of biological mediators which influence the tone and structure of the blood vessels and partly determine susceptibility of the vessel wall to atherogenesis.

Nitric oxide

Nitric oxide (NO) is synthesized by the endothelium from the amino acid L-arginine via the action of the enzyme NO synthase. NO diffuses to the underlying vascular smooth muscle where it activates soluble guanylate cyclase leading to a rise in cyclic GMP and causes vasorelaxation [23]. NO plays a vital role in the regulation of basal vascular tone and blood pressure. Organic nitrates such as glyceryl trinitrate are metabolized by the vasculature to NO and so act as an external source of NO and, in humans, it has long been recognized that glyceryl trinitrate profoundly alters the pulse pressure waveform, lowering the late systolic shoulder of the peripheral wave and shifting it into diastole [24]. More recently, glyceryl trinitrate has also been shown to decrease augmented pressure centrally [25] (Figure 2).

Thus, arterial stiffness and wave reflection may be, under the regulatory control of endogenous mediators such as NO and may provide a non-invasive surrogate marker of endothelial dysfunction. Support for this hypothesis comes from recent animal experiments where inhibition of NO synthase in the rabbit is associated with augmented wave reflection [26]. Infusion of acetylcholine, which stimulates endothelial release of NO, has the opposite effect, and this can be blocked by NO synthase inhibition [26] (Figure 2). In diabetes, a condition associated with endothelial dysfunction [27], abnormalities of the pulse wave consistent with increased vascular stiffness are detectable early in patients with no clinical evidence of cardiovascular disease [17]. Fish oil, which improves endothelial function in these patients [27], also decreases arterial stiffness [22].

Endothelial dysfunction develops with age [28, 29] and occurs earlier in men [28]. Decreased bioavailability of endogenous NO is found in premature ‘vascular ageing’ associated with a number of cardiovascular risk factors, such as hyperlipidaemia and diabetes. Here, functional changes in pulse waveform may be important for the development of atheroma and could potentially be reversible.

Endothelin

Endothelin-1 is a 21-amino-acid peptide produced by vascular endothelial and smooth muscle cells and is an extremely potent vasoconstrictor. It also plays a role in the regulation of basal vascular tone and blood pressure in humans [30]. For this reason, endothelin-1 is likely to influence pulse waveform. Indeed, plasma endothelin-1 concentration, as an index of endothelin-1 generation, shows a significant positive correlation with an ultrasound-determined index of aortic stiffness in patients with coronary artery disease [31].

Consequences of increased arterial stiffness

Left ventricular hypertrophy

In addition to being a marker for degenerative physical changes and dysfunctional regulatory processes, increased vascular stiffness may have important dynamic consequences. The pressure that the left ventricle works against is determined by arterial stiffness. While stiffer arteries enhance central aortic pressures, due to increased PWV and wave reflection, the effect on brachial pressure is often much less noticeable. The consequent increase in haemodynamic load may stimulate ventricular and vascular adaptive changes. Indeed, the increase in left ventricular mass seen in subjects with a dominant late systolic peak pressure appears to be directly related to the shape of the pressure waveform [32], and increasing age has been shown to induce left ventricular concentric remodelling in normotensive subjects [33].

Thus, vascular stiffness may determine left ventricular hypertrophy [34], an important independent risk factor for cardiovascular death. Indeed, early pulse wave reflection as a consequence of increased vascular stiffness may be the principal cause of left ventricular failure in patients with long-standing hypertension [35].

Stroke

Increased arterial stiffness may be associated with stroke either causally or as a marker for atherosclerosis. Arterial stiffness, as measured by the height of the dicrotic notch, was assessed in a large cohort of men and women in the Framingham study. Although systolic hypertension was significantly correlated with stroke, arterial stiffness assessed by pulse wave analysis was not [7]. However, this study only evaluated
changes in the peripheral pulse waveform and therefore could not exclude significant correlations between central augmented aortic pressure and stroke, especially since there is less increase in PWV in the upper limb than in the aorta in cardiovascular disease [9].

Heart failure
Chronic heart failure is increasingly common in the ageing population. Patients with chronic heart failure exhibit endothelial dysfunction [36], and decreases in NO could explain the increased vascular stiffness, and therefore the augmented systolic pressure, seen in this condition. In the non-failing heart, ventricular contraction can eject blood against this augmented pressure and there is no reduction in flow. However, when the heart fails, wave reflectance has less effect on pressure but more on flow, so systolic pressure is lower [37]. Ultimately, in severe chronic heart failure, the heart moves to function as a pressure source so there is almost no systolic pressure augmentation, but flow is markedly limited, with accompanying abbreviation of systole and premature closure of the aortic valve.

Atherosclerosis/coronary heart disease
Several workers have reported an association between atherosclerosis and arterial stiffness. In animal studies atherogenic diets can induce both arterial stiffness and atherosclerosis; both are reversible [38] but which is causal remains unclear. In humans with coronary artery disease, arterial stiffness is also increased as measured by both invasive and non-invasive techniques [39–41]. It has been suggested that...
stiffer arteries are more susceptible to intimal injury by pulsatile pressure and that this injury is a precursor for atheroma [42]. Endothelial dysfunction may contribute to arterial stiffness and atherosclerosis through structural alteration because endothelin-1, produced in excess, is a co-mitogen [30] and NO, the production of which is decreased, has major anti-mitogenic properties [43].

**Therapeutic intervention**

The possibility of reversing vascular stiffness by therapeutic intervention has received little attention because vascular stiffness has been thought to be determined by physical, irreversible changes. Failure of some anti-hypertensive therapy to reduce cardiovascular mortality predicted by changes in conventionally measured blood pressure may be because they fail to decrease arterial stiffness. Indeed, β-blockers augment central aortic pressure, despite reducing brachial arterial pressure [20], via enhanced wave reflection from the periphery. Wave reflection from the periphery is reduced by vasodilator agents, which produce a larger reduction in central systolic pressure than is apparent from pressure measurements in the brachial artery. Pulse wave analysis may, therefore, be of value in the accurate assessment of response to and benefits from therapy. The concept that vascular stiffness is determined in part by endothelial function suggests that drugs which modulate the endothelin and NO systems may have beneficial effects on vascular stiffness.

**Angiotensin-converting enzyme (ACE) inhibitors**

ACE inhibitors, by inhibiting breakdown of bradykinin [44], may increase NO production and decrease vascular stiffness in addition to their antihypertensive actions. Angiotensin II stimulates production of superoxide from the vascular endothelium [45]. Superoxide reacts with NO to inactivate it and form peroxynitrite. ACE inhibition may therefore increase the bioavailability of endogenous NO by inhibiting superoxide production locally. These endothelial actions of ACE inhibitors may explain their success in the regression of left ventricular hypertrophy. ACE inhibition reverses abnormal endothelial function in the coronary circulation of patients with angiographically proven coronary atheroma [46]. Recently, ACE inhibition has also been shown to decrease aortic stiffness, as assessed by PWV [47]. In a further study, involving hypertensive patients with end-stage renal failure, treatment with an ACE inhibitor reduced both peripheral wave reflectance and PWV [48], although in this study the decrease in PWV was due to decreased blood pressure. Thus, ACE inhibition may bring special benefit to elderly subjects through reducing both blood pressure and vascular stiffness.

**Lipid lowering therapy**

Hypercholesterolaemia is associated with endothelial dysfunction and decreased production of endogenous NO [49, 50]. A recent study showed a significant increase in the augmentation of central systolic pressure in hypercholesterolaemic subjects relative to matched controls (M. Monagani, personal communication). Since blood pressure was similar in the two groups this suggests an increase in vascular stiffness in the hypercholesterolaemics which may be mediated by decreases in NO. Cholesterol reduction improves endothelial function [50, 51], increasing the bioavailability of NO. Decreases in cholesterol may also be associated with small reductions in blood pressure [52]. This may explain the unexpected reduction in stroke in a recent study of patients following myocardial infarction [53], although there was no significant change in blood pressure in this study. Alternatively, this finding could be explained by reduced vascular stiffness following cholesterol reduction.

**Oestrogens and antioxidant therapy**

Oestrogen increases basal endothelial NO release in post-menopausal women [54] and has also been shown to decrease aortic stiffness [55]. Antioxidants, such as vitamin E, have been shown to inhibit oxidation of low-density lipoprotein (LDL) cholesterol [56] and oxidized LDL is a potent inhibitor of endothelial function. Indeed, in hypercholesterolaemic rabbits, vitamin E both inhibits LDL oxidation and improves endothelial function and arterial stiffness [26, 57]. Antioxidants have also been associated with decreases in blood pressure [58], which may be due to increasing availability of NO by scavenging free radical species that would otherwise inactivate NO [59]. As yet, there are no data on whether the reduction in systemic blood pressure observed with antioxidants is associated with a decrease in vascular stiffness.

**Endothelin receptor antagonists**

No studies have directly addressed the therapeutic value of endothelin antagonists in reducing arterial stiffness and wave reflection. However, given what we already know about the beneficial actions of endothelin receptor antagonists on haemodynamics in chronic heart failure [60] and hypertension [61], it would not be unreasonable to explore their effects on the pulse wave.
Conclusions

Arterial stiffness, through its effect on the pulse wave and central aortic pressure, may be a key determinant of increased cardiovascular risk. Enhanced vascular stiffness may arise not only as a result of age-related and irreversible degenerative arteriosclerotic changes, but also as a result of reversible endothelial dysfunction. Such changes may occur early in the course of diseases associated with premature vascular ageing. Thus, pulse wave analysis may provide a simple, reliable, non-invasive method for detecting endothelial dysfunction and cardiovascular risk at a stage when therapeutic intervention may be of benefit.

Perhaps, it stands to reason that interpretation of the full pulse waveform should provide more useful information than merely using extremes of pressure provided by sphygmomanometry. However, this aspect of cardiovascular physiology has been largely overlooked since its original description by Mohamed. Reversing vascular stiffening associated with age and disease presents a promising and important challenge for the future.

References

3. Mahomed FA. The etiology of Bright's disease and the pre-albuminuric stage. Med Chir Trans 1874; 57: 197-228.


