Some mechanical aspects of arterial aging: physiological overview based on pulse wave analysis

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***Abstract*:** Aging has a striking impact on the arterial structure and function. The principal structural change with age is medial degeneration that leads to a progressive stiffening of the large elastic arteries. Large artery stiffening increases aortic systolic and pulse pressures through an increase in the forward incident wave and an early return of the backward reflected wave. Peripheral muscular arteries/arterioles are only minimally affected in structure by aging itself, but impaired vasomotor function can alter their impedance properties and thereby increase reflection magnitude. An augmented aortic pressure due to enhanced wave reflection increases wasted left ventricular effort and causes cardiac hypertrophy. Increased pulsatile pressure and flow stresses extend to the vulnerable microcirculation of vasodilated organs such as the brain and kidneys, and can predispose to cerebral lacunar infarction and albuminuria. Although most currently available vasodilators appear to have little direct effect on degenerated elastic arteries, they can act instead on less-degenerated muscular arteries to markedly reduce peripheral wave reflection magnitude and central aortic pressure, and thus contribute to the regression of left ventricular hypertrophy. Further studies are necessary to examine whether the effect of vasodilator therapy on reducing wave reflection contributes similarly to the prevention of microvascular damage in the brain and kidneys.

***Keywords*:** aging, arteriosclerosis, wave reflection, blood pressure, hypertrophy, microcirculation, pulse, pharmacology

Introduction

The number of elderly people is rapidly increasing, and nearly 20% of all people living in developed countries are now older than 65 years of age. Aging has a striking impact on the morbidity and mortality of cardiovascular disease. Meta-analysis data from over one million adults have shown that the risk of ischemic heart disease mortality is increased at least twofold with every higher decade of aging [Lewington *et al*. 2002]. The systolic pressure rises progressively while the diastolic pressure tends to decrease with advancing age, and thus pulse pressure widens [Burt *et al*. 1995]. Arterial stiffening with age is primarily responsible for the widened pulse pressure and increased prevalence of isolated systolic hypertension in elderly people [Nichols and O'Rourke, 2005]. Coexistence of aging and hypertension has an even greater deleterious impact on cardiovascular prognosis [Lewington *et al*. 2002].

A better understanding of the mechanisms underlying arterial aging must be attained to develop strategies aimed at limiting reversible and irreversible cardiovascular damage in the elderly. The present review discusses arterial aging from the mechanical view that lifelong repetitive pulsatile pressure stress causes progressive degeneration of arterial walls. This review will also deal with the deleterious consequences for vital organs such as the heart, brain, and kidneys, and potential strategies for its treatment and prevention.

Anatomical and physiological basis of arterial system

The structure of the arterial tree in humans consists of three different parts. The elastic aorta is the most proximal and largest part, the muscular arteries are the intermediate part, and the arterioles are the most distal and smallest part. The entire arterial tree acts as both a conduit

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(to distribute blood from the heart to the capillaries) and cushion (to change pulsatile flow generated by cardiac intermittent contraction to steady flow). Different parts of the arterial tree play considerably different roles as conduit and cushion; large elastic arteries work predominantly as cushions, while small arteries and arterioles work predominantly as conduits.

Hales first created a conceptual model explaining the function of the human arterial system in the eighteenth century, which is currently well-known as the Windkessel model [Hales, 1733]. He compared the arterial system with the contemporary fire engine, representing large arteries as the air-filled dome (Windkessel), the medium-sized distributing arteries as the fire hose, and small arterioles as the nozzle. He thus implied that the arterial functions of cushion, conduit, and resistance reside in the proximal elastic arteries, muscular arteries, and peripheral arterioles, respectively.

This classic model is still valid since it clearly shows the fact that the arterioles are responsible for the greatest components of systemic peripheral resistance. Indeed, the fall of the mean blood pressure along the arterial tree is only trivial from the proximal aorta down to the intermediate-sized muscular arteries, but it becomes abruptly manifest over a very short length of the peripheral arterioles [Bohlen, 1986; Schleider, 1918]. This model is also correct in that the large elastic arteries are the major sites playing the cushioning role. However, some important features of arterial function are overlooked in this simplified model. In the real arterial system, (a) the respective functions of cushion and conduit are not confined to particular arteries but actually combined in the whole arterial system; and (b) the transmission of the pulsatile pressure wave from the heart to the periphery causes the phenomenon of 'wave reflection'.

More realistic models proposed in the decades between the 1930s and 1950s were referred to as 'transmission line' models, in which the arterial tree was likened to an electrical transmission line [McDonald and Taylor, 1959; Womersley, 1957; Hamilton and Dow, 1939]. The arterial system of this model is represented as a single distensible tube in which both the conduit and cushion functions are combined. The proximal end of the tube corresponds to the central aorta, and the distal end to the high-resistance arterioles. The pressure (electrical) wave generated by cardiac ejection travels along this tube from the proximal end to the distal end, where this forward wave is reflected back. The use of such tubular models makes it possible to explain the various phenomena that are observed in the actual human arterial system but had not been interpretable by the classic Windkessel model. These include (a) a secondary pressure wave in diastole or late systole; and (b) amplification of the pressure pulse from the proximal aorta to the distal muscular arteries; they are now readily explicable by the concept of wave transmission and reflection [Hashimoto and O'Rourke, 2009; Nichols and O'Rourke, 2005] (see below).

Effect of age on arterial structure

The effect of age is most obvious in the structure of the large elastic arteries. The principal changes include (a) increased stiffness (decreased distensibility), (b) increased wall thickness, and (c) increased lumen diameter. Hypertension can cause additional structural changes in microvessels, such as hypertrophy of the vascular smooth muscle, vascular remodeling, and decreased vascularity (rarefaction) [Rizzoni *et al*. 2003; Vicaut, 1999]. Increased stiffness of elastic arteries with age has been attributed primarily to the degeneration of the medial layer of the arterial walls [Nichols and O'Rourke, 2005]. The media, which is mainly responsible for distensible properties of arterial walls, consists of elastic fibers, smooth muscle cells, collagen fibers, and ground substance. The age-dependent change in these medial components is explicable on the basis of 'cyclic stress'; repetitive pulsatile stress due to cardiac intermittent contraction causes gradual thinning, splitting, fraying and fragmentation of the load-bearing elastic fibers, which are accompanied by increases in collagen fibers and ground substance [Avolio *et al*. 1998]. Long-standing cyclic stress eventually leads to a loss of the original orderly arrangement of elastic lamellae and other components of the arterial wall, thus resulting in structural stiffening through transfer of stress from more distensible elastic fibers to less distensible collagenous fibers. Such degeneration of the media with advancing age is generally referred to as 'arteriosclerosis.'

This term 'arteriosclerosis' has to be differentiated from 'atherosclerosis' that affects mainly arterial intima rather than the media through an endothelial inflammatory process with lipid accumulation to cause luminal stenosis or occlusion,

although these two lesions often coexist in aged arteries. Arteriosclerotic lesions tend to be seen diffusely in systemic elastic arteries, whereas atherosclerotic lesions are located in particular, susceptible (vulnerable) elastic and muscular arteries (e.g. carotid bifurcation and coronary arteries). The histological changes in the large arteries due to hypertension are essentially similar to those with aging (i.e. arteriosclerosis) but they appear earlier in life, indicating that hypertension can be regarded as an accelerator of arterial aging [Taddei *et al*. 1997; Carlson *et al*. 1970].

In contrast to the large elastic arteries, the medium-sized muscular arteries are hardly affected by aging [Heijden-Spek *et al*. 2000; Boutouyrie *et al*. 1992; Ho, 1982]. This is likely due to the fact that the muscular arteries are less distensible than the elastic arteries and therefore are exposed to much less cyclic stretch. Such differences in the aging effects between elastic and muscular arteries cause a gradual disappearance of the elastic non-uniformity of the arterial system between the proximal and distal sites, which is normally observed in infancy and adolescence. This relates to the progressive decrease in pressure pulse amplification [McEniery *et al*. 2005; Wilkinson *et al*. 2001] and impairment in ventricular-vascular interaction [Westerhof and O'Rourke, 1995] with advancing age (see below).

Increased wall thickness of the large elastic arteries with age depends largely on intimal hyperplasia with or without atherosclerotic plaques [Virmani *et al*. 1991]. Numerous studies have demonstrated an age-dependent increase in carotid intima-media thickness [Lakatta *et al*. 2003; Tanaka *et al*. 2001; Nagai *et al*. 1998]. The possible mechanisms responsible for intimal thickening include atherosclerosis, local pressure elevation, and biochemical alterations with age [Wang *et al*. 2007]. The dilated wall lumen of elastic arteries is also a typical feature of vascular aging [Vasan *et al*. 1995]. The arterial dilatation probably results from degenerated and fractured elastic lamellae leading to a weakened arterial wall. According to the law of LaPlace, the stress on the arterial wall becomes even greater as a consequence of a dilated lumen. [Folkow, 1987]. Therefore, the dilatation of the arterial lumen and the degeneration of the arterial wall create a vicious cycle and thereby accelerate the aging process further.

Aging is related to not only the mechanical but also the biological properties of arteries. For instance, nitric oxide (NO) availability and endothelium-dependent vasodilation have been shown to decrease progressively with increasing age [Taddei *et al*. 2001]. Biomolecular mechanism is also an important aspect of arterial aging, but is beyond the scope of this review; it has been extensively described elsewhere by expert investigators [Greenwald, 2007; Najjar *et al*. 2005; Lakatta *et al*. 2003].

Clinical evaluation of arterial aging

Several noninvasive measurements have been used to evaluate elastic properties of the arterial wall [Laurent *et al*. 2006]. The most widely used method is the measurement of pulse wave velocity (PWV). PWV is calculated from the distance between two recording sites (D) and the time delay measured between the feet of the two pulse waveforms (t): $\mathrm{PWV} = D/t$. The relationship between PWV and wall elasticity is explained by the Moens-Koteweg equation: $\mathrm{PWV} = Eh/2R\rho$, where E is Young's elastic modulus; h, the wall thickness; R, the internal radius; and ρ is the blood density. This simple equation means that the stiffer the artery, the faster the PWV. According to the Water-hammer formula, PWV is directly related to characteristic impedance (Z_c), an index of the resistance to pulsatile flow that would be seen in the absence of wave reflection, although Z_c has a greater dependence on arterial diameter than PWV [Mitchell *et al*. 2003]. PWV can provide information on any 'regional' arterial segment, but much interest has been directed toward the carotid-femoral region because most elastic arteries reside there. In Japan, brachial-ankle PWV is also used on the ground that it correlates closely with carotid-femoral PWV [Yamashina *et al*. 2002]. A substantial body of evidence has shown the carotid-femoral PWV [McEniery *et al*. 2005; Avolio *et al*. 1983] and brachial-ankle PWV [Hashimoto *et al*. 2005a; Tomiyama *et al*. 2003] to increase with advancing age. The PWV is associated with various cardiovascular risks and predicts cardiovascular morbidity and mortality, as summarized in a recent review [Hashimoto and O'Rourke, 2008; O'Rourke and Hashimoto, 2008].

In contrast to the regional assessment with PWV, more local assessment of arterial stiffness can be made with simultaneous measurements of pulsatile pressure and diameter changes. The recently

developed echo-tracking method makes it possible to evaluate minute movement of arterial walls with pressure pulsation [Hoeks *et al*. 1990]. Various indices can be calculated from these, including distensibility coefficient, incremental elastic modulus, and stiffness index beta [Bussy *et al*. 2000; Liao *et al*. 1999; Laurent *et al*. 1994; Hoeks *et al*. 1990]. So far, however, the outcome data on these local stiffness indices are quite limited. This technique is indicated for detailed research on vascular pathophysiology rather than for routine use in clinical practice [Laurent *et al*. 2006].

Another type of methodology for evaluating arterial properties is pulse waveform analysis (PWA). Indices calculated from this analysis reflect 'systemic' arterial properties, because the entire arterial structure and function determines the pulse waveform through pressure transmission and reflection phenomena. The augmentation index (AIx) is the most widely used among several waveform parameters, which will be dealt with subsequently in association with blood pressure. A PWA can be applied to not only pressure, but also flow, data in terms of its time- and frequency-domain characteristics [Michelson *et al*. 2007; Hirata *et al*. 2006]. Digital photoplethysmogram (PTG) is the simplest method for flow waveform analysis, and the second derivative wave of digital PTG shows a significant change with increasing age [Hashimoto *et al*. 2005a; Hashimoto *et al*. 2002; Millasseau *et al*. 2000; Takazawa *et al*. 1998].

Effect of age on blood pressure

Wave reflection

According to the 'transmission line' mechanism, the pressure pulse generated by cardiac ejection propagates along the arterial tree forwards from the central aorta to the peripheral high-resistance arterioles, where it is reflected, and then it propagates backwards to the heart. Because the speed of propagation (i.e. PWV) is high enough for the pulse to return within the same cardiac cycle up to the central aorta, the reflected (backward) wave overrides the incident (forward) wave to create an actual waveform. Aortic AIx is generally defined as the ratio of the pressure augmented by the reflected wave (augmented pressure, AP) to pulse pressure (PP): $\text{AIx} = \text{AP} \div \text{PP} \times 100$ (%). The aortic AIx is often measured noninvasively by estimating the aortic waveform from the radial one with a generalized transfer function [Pauca *et al*. 2001; Karamanoglu *et al*. 1993]. Alternatively, AIx can be determined directly from the carotid or radial waveform [Hashimoto *et al*. 2006; 2005b; Takazawa *et al*. 1995; Kelly *et al*. 1989a].

The AIx has been generally considered to be a global index of wave reflection, but actually it is composite and determined by both the magnitude and timing of the reflected wave. Figure 1 shows the effects of peripheral wave reflection on aortic pressure waveforms. Normally in adults over 40 years of age, the reflected wave augments blood pressure in late systole and causes a positive aortic AIx (Figure 1a). A pathological increase in the AIx can occur as a result of increased magnitude (Figure 1b) and/or hastened timing (Figure 1c) of the reflected wave.

The reflection magnitude depends largely on the impedance properties of the peripheral reflecting sites, and partially on the (electrical) damping of wave transmission and spatial dispersion of reflecting sites [Nichols and O'Rourke, 2005]. It is usually quantified as the ratio of the height of the reflected wave to the height of the incident wave [Westerhof *et al*. 2006]. The reflection magnitude is increased by vasoconstriction and reduced by vasodilation [O'Rourke and Taylor, 1966]. On the other hand, reflection timing is determined by the distance and PWV between the central aorta and peripheral reflecting sites. It is generally measured as the round-trip travel time (T_r), that is the delay between the initial upstroke and the inflection point of the aortic pulse wave [Nichols, 2005; Mitchell *et al*. 2004]. The T_r is shown to correlate closely (inversely) with the carotid-femoral PWV, indicating its great dependence on the elastic properties of the large arteries [London *et al*. 1992]. From this viewpoint, one can state that the reflection magnitude depends mainly on the peripheral small arterial/arteriolar properties, whereas the reflection timing depends mainly on the proximal large arterial properties [Kelly *et al*. 2001]. Specifically, peripheral vascular constriction (responsible for systemic hypertension) enhances the reflection magnitude and thereby increases AIx (Figure 1b); in contrast, large artery stiffening (due primarily to aging and secondarily to increased distending pressure) can induce early return of wave reflection and thereby increase the AIx (Figure 1c).

Numerous studies have shown the clinical usefulness of the aortic AIx in evaluating cardiovascular

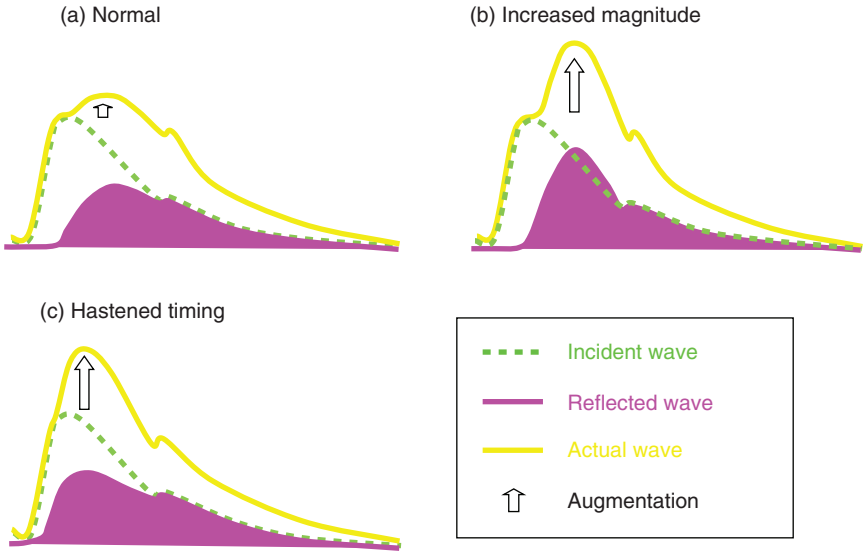

Figure 1. Effects of the peripheral wave reflection magnitude and timing on the aortic pressure waveform. An increase in late-systolic pressure augmentation is attributable to an increase in reflection magnitude (b) and/or to early return of the wave refection (c).

risk and predicting the prognosis, and have been reviewed elsewhere [Hashimoto and O'Rourke, 2008]. The AIx increases progressively with age up to 60 years, but it flattens thereafter [Wojciechowska *et al.* 2006; McEniery *et al.* 2005; Hashimoto *et al.* 2005a; Mitchell *et al.* 2004]. The underlying mechanism for the flattening of the AIx, in contrast to the continuous increase in the carotid-femoral PWV, is still controversial, but it might be attributable in part to change in the left ventricular flow wave as a consequence of impaired contractility [O'Rourke and Hashimoto, 2006]. It should be of note that the AIx might underestimate the 'true' reflection magnitude, because the peak of the reflected wave (that determines the reflection magnitude) differs in time from the peak of the augmented pressure (that determines the AIx) [Mitchell, 2006].

Brachial versus central pressure: Pulse amplification

As described above, the pressure waveform is a composite of the incident wave (dependent on characteristic impedance and stroke volume) and the reflected wave (arising mainly from the lower body). This principle can be applied to not only the aortic but also the brachial waveforms, although these waveforms are quite different in appearance. The difference between these waveforms is attributed in some part to the difference in shape of the incident wave that forms the first (early) systolic peak; the amplitude of the incident wave is normally greater in the brachial artery than in the aorta because of increasing stiffness towards the periphery (i.e. non-uniform elasticity). The waveform difference is also attributed in other part to the effect of the reflected wave that forms the second (late) systolic peak; normally in middle-aged adults, aortic maximum pressure (i.e. aortic systolic pressure) corresponds to the second peak affected by wave reflection, whereas brachial maximal pressure (i.e. brachial systolic pressure) corresponds to the first peak not affected by wave reflection [Vlachopoulos *et al.* 2001; Kelly *et al.* 1989b].

The ratio of brachial pulse pressure to aortic pulse pressure is often called the 'pulse amplification.' Such 'broad-sense' pulse amplification actually comprises a summation of two different components: (a) the 'narrow-sense' or 'non-augmented' [Wilkinson *et al.* 2001] amplification, which means the forward (incident) wave amplification from the aorta to the brachial artery; and (b) wave reflection-induced augmentation, which normally has much greater effect on the aortic than brachial pulse pressure. The former component increases pulse amplification, whereas the latter component reduces pulse amplification.

It is well known that pulse amplification decreases with advancing age [McEniery *et al.* 2005; Wilkinson *et al.* 2001]. On the basis of the two components responsible for pulse amplification, this age-related phenomenon could be

explained theoretically by two potential mechanisms: (a) a decrease in 'narrow-sense' amplification of the incident wave; and (b) an increase and/or early return of the reflected wave. In this regard, Wilkinson *et al.* demonstrated that the latter (i.e. increased or early wave reflection), but not the former, is actually associated with decreased pulse amplification in the elderly [Wilkinson *et al.* 2001].

Studies have shown that peripheral (brachial) pulse pressure is an important predictor of cardiovascular events [Blacher *et al.* 2000]. Increased peripheral pulse pressure as often seen in elderly people is likely attributable primarily to increased central aortic stiffness rather than peripheral wave reflection [Mitchell *et al.* 2008]. Nevertheless, this does not rule out, but may rather imply, the involvement of enhanced wave reflection in cardiovascular prognosis, given that central pulse pressure is more predictive than peripheral pulse pressure [Jankowski *et al.* 2008; Roman *et al.* 2007] and that pulse amplification becomes more dependent on wave reflection with increasing age [Wilkinson *et al.* 2001].

Arterio-ventricular interaction and its change with age

The timing of wave reflection is closely related to the efficiency of the cardiac function. Normally in adolescents, wave reflection returns to the heart in early diastole, augments diastolic pressure, and thus increases coronary blood flow. Such ideal 'tuning' between the heart and arterial system, however, is fragile and disappears gradually with advancing age. Large artery stiffening causes an early return of the wave refection as well as an increase in the incident wave, which leads to an elevation of systolic pressure and a reduction in diastolic pressure. The former increases the myocardial oxygen demand and induces a hypertrophic response [Watabe *et al.* 2006], while the latter reduces the oxygen supply, both predisposing to myocardial ischemia and heart failure [O'Rourke and Hashimoto, 2006]. Arterial stiffening with concomitant ventricular stiffening may account for the increased prevalence of heart failure with preserved ejection fraction in elderly people [Redfield *et al.* 2005].

With respect to the mechanisms for impaired vascular-ventricular interaction, emphasis could be placed not only on the timing but also the magnitude and systolic duration of the wave reflection. An untreated hypertensive population (mean age of 55 years) showed a relationship between left ventricular hypertrophy and wasted effort (ΔE_w), that is an extra workload for the left ventricle to generate during ejection to overcome the augmented pressure due to wave reflection and is calculated as $\Delta E_w = 2.09 \times AG \times (ED - T_r)$, where AG is the augmented pressure, ED is ejection duration, and $(ED - T_r)$ means the systolic duration of the reflected wave (Figure 2) [Hashimoto *et al.* 2008a]. ΔE_w as well as the aortic systolic pressure and AIx were associated with hypertrophy, whereas PWV and T_r were not. This finding indicates, at least in patients with relatively early-stage and yet untreated hypertension, enhanced peripheral wave reflection can cause left ventricular hypertrophy even without accompanying large artery stiffening or early wave return [Hashimoto *et al.* 2006].

Effect of arterial aging on microvascular damage

Large artery stiffening may also be associated with microvascular damage of the brain and kidneys [O'Rourke and Hashimoto, 2006; O'Rourke and Safar, 2005; Safar 2004]. Normally in young people with distensible large arteries, pressure pulsation is absorbed in the upstream arteries so that the microvessels are perfused with steady flow. However, in elderly people with stiff large arteries, the pulsations are not completely absorbed so that the microvascular walls are exposed to pusatile pressure and flow stress. Such stress is markedly increased in the cerebral and renal vascular beds, because of their low constrictor tone [Nichols and O'Rourke, 2005]. The cerebral perforating arteries and renal glomerular capillaries may be particularly susceptible to these hemodynamic alterations due to their distinctive anatomical features [Ito *et al.* 2009]. This hypothesis was tested in a cross-sectional survey of the Japanese general population, which showed that the brachial-ankle PWV is associated with cerebral asymptomatic lacunar infarction [Hatanaka *et al.* 2006] and renal albuminuria [Ishikawa *et al.* 2008] independent of conventional risk factors.

A few previous studies have shown an interrelation between the microvascular damage of these different target organs (i.e. brain and kidney) in hypertension and with aging, although the mechanism remained unknown [Wada *et al.* 2007; Ravera *et al.* 2002]. A similar cerebro-renal interrelation has been also observed in a general population between lacunar infaction and

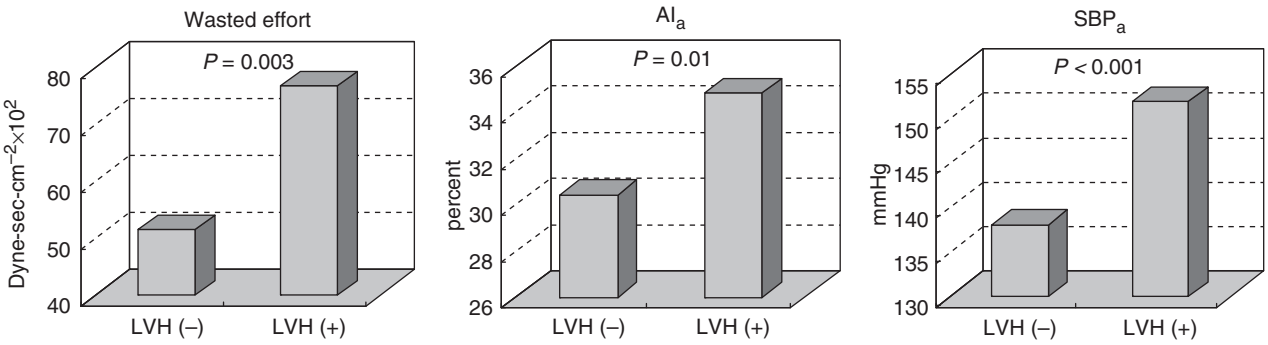

Figure 2. Association between various hemodynamic load parameters and left ventricular hypertrophy (LVH) in patients with untreated hypertension ($n = 98$). There were significant differences in wasted left ventricular effort, aortic augmentation index (AI_a) and aortic systolic blood pressure (SBP_a) between two groups with (+) and without (-) LVH [Hashimoto *et al.* 2008a]. Reproduced with permission.

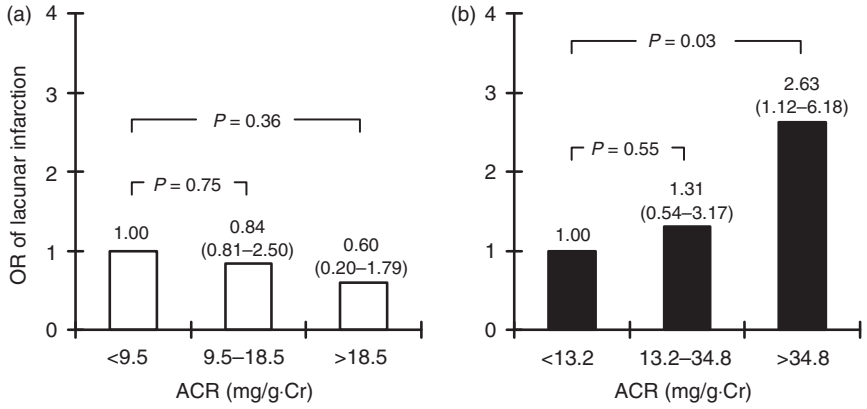

Figure 3. Influence of arterial stiffness on the relationship between cerebral lacunar infarction and albuminuria in a general population. Odds ratio (OR) for lacunar infarction was compared among the tertile groups of urinary albumin-to-creatinine ratio (ACR) separately in a) subjects with a low brachial-ankle PWV (<16.1 m/s, $n = 176$, left) and in b) subjects with a high brachial-ankle PWV (≥16.1 m/s, $n = 175$, right). ORs were adjusted for age, gender, 24-hour mean arterial pressure, serum creatinine, medication for hypertension, diabetes and smoking. Numbers in parentheses are 95% CI [Hashimoto *et al.* 2008c]. Reproduced with permission.

albuminuria, but only in the presence of increased PWV (Figure 3) [Hashimoto *et al.* 2008c]. This result suggests that large artery stiffening plays an important and pivotal role in connecting microvascular impairments of the brain and kidney. Naturally, further prospective studies are necessary to clarify whether large artery stiffening is primarily responsible for, or alternatively a consequence of, the simultaneous progression of microvascular damage in various target organs with advancing age and coexisting hypertension.

Pharmacological treatment and prevention of arterial aging

As mentioned above, the large elastic arteries and small muscular arteries/arterioles play different roles in regulating reflection magnitude and timing. This difference is apparent in pharmacological effects. The administration of nitroglycerine (or angiotensin II) has been shown to change the aortic AIx independently of PWV in healthy men [Kelly *et al.* 2001], indicating that vasoactive drugs can change the reflection magnitude irrespective of its timing. Similar findings on the dissociation between the AIx and PWV responses were observed in the ASCOT-CAFÉ trial [Williams *et al.* 2006], in which the amlodipine/perindopril arm showed a lower aortic AIx than the atenolol/thiazide arm during a 6-year period despite a similar trend for PWV. In a recent study examining the respective changes in the reflection magnitude, T_r, and PWV during 1 year of treatment with vasodilator drugs including

angiotensin-receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), and calcium channel blockers (CCBs), only a marginal correlation was observed between the changes in the reflection magnitude and T_r [Hashimoto *et al.* 2008b]. All these findings can probably be explained by the fact that most currently available vasodilators act primarily on the peripheral muscular arteries and arterioles to reduce wave reflection (as shown in reflection magnitude and AIx changes), whereas their effect on the large elastic arteries (as shown in PWV and T_r changes) is largely passive and secondary to the lowered distending pressure. In fact, most [Williams *et al.* 2006; Asmar *et al.* 2001], if not all [Guerin *et al.* 2001], studies have failed to show a direct (i.e. blood pressure-independent) effect of vasodilators on PWV.

There is substantial evidence that different antihypertensive drugs have different effects on peripheral wave reflection, as summarized elsewhere [Hashimoto and O'Rourke, 2008]. Most have shown that vasodilator therapy with ARBs, ACEIs and CCBs is more effective in reducing the AIx and central blood pressure than non-vasodilator therapy with β-blockers and diuretics. These preferable effects of vasodilators on reducing peripheral wave reflection may be particularly beneficial for prevention of cardiovascular disease. In the above-mentioned ASCOT-CAFÉ study [Williams *et al.* 2006; Dahlof *et al.* 2005], the lowered aortic augmented pressure, rather than aortic forward pressure, contributed to a lower incidence of cardiovascular events in the amlodipine/perindopril arm. In another study, a reduced reflection magnitude, but neither increased T_r nor decreased PWV, was directly associated with left ventricular mass reduction during vasodilator treatment for hypertension (Figure 4) [Hashimoto *et al.* 2008b]. Considering these results with previous findings [Hashimoto *et al.* 2007], the potential mechanism could be that vasodilator therapy lowers the central aortic pressure primarily through reducing the reflection magnitude at the sites of peripheral small muscular arteries/arterioles (rather than through delaying the reflection timing or altering the characteristic impedance in the proximal elastic arteries), contributing to the regression of LV hypertrophy and eventually to the decline of cardiac events.

It should be noted that vasodilators not only act locally on the susceptible arteries of vital organs (such as the heart, brain, and kidneys), but also act systemically on arteries of all parts of the body (including skeletal muscles in the lower body). As described above, the latter action seems quite important in reducing the tensile and shear stress to these vulnerable vital organs indirectly through decreasing wave reflection arising from the whole body. This also provides a basis for the view that the targets of effective therapy for arterial aging can be directed to the peripheral muscular arteries with preserved structure rather

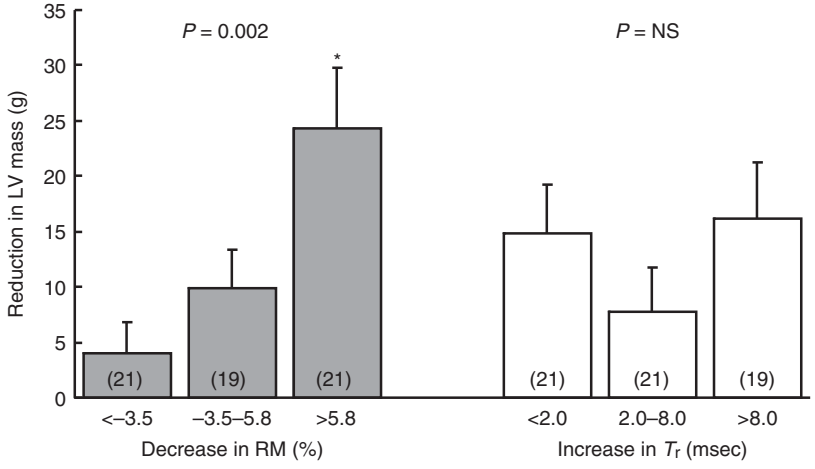

Figure 4. Relationship between the changes in wave reflection and left ventricular (LV) mass during 1-year vasodilator treatment for hypertension. Subjects were classified into tertile groups according to the changes in reflection magnitude (RM, left) or round-trip travel time (T_r, right). Data are shown as means ± SE, and the number of subjects in parenthesis. P values for trend are based on analysis of variance. $*p < 0.05$, compared with the lowest tertile [Hashimoto *et al.* 2008b]. Reproduced with permission.

than to the proximal elastic arteries with inevitable degeneration [O'Rourke and Hashimoto, 2006; Boutouyrie *et al*. 1992].

In the future, novel drugs might act directly on the large elastic arteries to prevent or even reverse the age-related degeneration. The possible mechanisms for such pharmacological repair of the large arterial wall could include a reduction in collagen content or cross-linking, an increase in the elastin: collagen ratio, and a change in the connections of smooth muscle cells to the extracellular matrix through the fibronectin-integrin relationship [Struijker-Boudier *et al*. 2003; Laurent *et al*. 2002], although there is some evidence that currently available ACEIs and ARBs might possess similar pharmacological properties [Shargorodsky *et al*. 2008; Tropeano *et al*. 2006]. The formation of advanced glycation end-products (AGE) is responsible for arterial stiffening with age [Corman *et al*. 2001], and algebrium (ALT-711) that breaks AGE cross-links, might have the potential to reverse such aging process [Kass *et al*. 2001]. Dual inhibition of neutral endopeptidase and angiotensin-converting enzyme with the vasopeptidase inhibitor omapatrilat could also have a reversing effect on conduit artery stiffening, independent of its effect on the mean arterial pressure [Mitchell *et al*. 2002]; however, this drug was not approved by the US Food and Drug Administration due to angioedema safety concerns. Clearly, the clinical efficacy and applicability of other new drugs must be further examined by carefully designed trials.

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Conflict of interest statement

None declared.

References

Asmar, R.G., London, G.M., O'Rourke, M.F. and Safar, M.E. (2001) Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose peridopril/indapamide combination in hypertensive patient: A comparison with atenolol. *Hypertension* 38: 922–926.

Avolio, A.P., Chen, S.G., Wang, R.P., Zhang, C.L., Li, M.F. and O'Rourke, M.F. (1983) Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. *Circulation* 1: 50–58.

Avolio, A., Jones, D. and Tafazzoli-Shadpour, M. (1998) Quantification of alterations in structure and function of elastin in the arterial media. *Hypertension* 32: 170–175.

Blacher, J., Staessen, J.A., Girerd, X., Gasowski, J., Thijs, S., Liu, L. *et al.* (2000) Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. *Arch Intern Med* 160: 1085–1089.

Bohlen, H.G. (1986) Localization of vascular resistance changes during hypertension. *Hypertension* 8: 181–183.

Boutouyrie, P., Laurent, S., Benetos, A., Girerd, X.J., Hoeks, A.P. and Safar, M.E. (1992) Opposing effects of ageing on distal and proximal large arteries in hypertensives. *J Hypertens* 10(suppl 6): S87–S91.

Burt, V.L., Whelton, P., Roccella, E.J., Brown, C., Cutler, J.A., Higgins, M. *et al.* (1995) Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-91. *Hypertension* 25: 305–313.

Bussy, C., Boutouyrie, P., Lacolley, P., Challande, P. and Laurent, S. (2000) Intrinsic stiffness of the carotid artery wall material in essential hypertensives. *Hypertension* 35: 1049–1054.

Carlson, R.G., Lillehei, C.W. and Edwards, J.E. (1970) Cystic medial necrosis of the ascending aorta in relation to age and hypertension. *Am J Cardiol* 25: 411–415.

Corman, B., Duriez, M., Poitevin, P., Heudes, D., Bruneval, P., Tedgui, A. *et al.* (1998) Aminoguanidine prevents age-related arterial stiffening and cardiac hypertrophy. *Proc Natl Acad Sci USA* 95: 1301–1306.

Dahlof, B., Sever, B., Poulter, N.R., Wedel, H., Beevers, D.G., Caulfield, M. *et al.* (2005) Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 366: 895–906.

Folkow, B. (1987) Structure and function of the arteries in hypertension. *Am Heart J* 114: 938–948.

Greenwald, S.E. (2007) Aging of the conduit arteries. Ageing of the conduit arteries. *J Pathol* 211: 157–172.

Guerin, P., Blacher, J., Pannier, B., Marchais, S.J., Safar, M.E. and London, G.M. (2001) Impact of aortic stiffeness attenuation on survival of patients in end-stage renal failure. *Circulation* 103: 987–992.

Hales, S.(1733) *Statistical essays, containing Haemastaticks*, Hafner Publishing: New York.

Hamilton, W.F. and Dow, P. (1939) An experimental study of the standing waves in the pulse propagated through aorta. *Am J Physiol* 125: 48–59.

Hashimoto, J., Chonan, K., Aoki, Y., Nishimura, T., Ohkubo, T., Hozawa, A. *et al.* (2002) Pulse wave velocity and the second derivative of the finger photoplethysmogram in treated hypertensive patients: their relationship and associating factors. *J Hypertens* 20: 2415–2422.

Hashimoto, J., Watabe, D., Kimura, A., Takahashi, H., Ohkubo, T., Tostune, K. *et al.* (2005a) Determinants of the second derivative of the finger photoplethysmogram and brachial-ankle pulse wave velocity: the Ohasama study. *Am J Hypertens* 18: 477–485.

Hashimoto, J., Watabe, D., Ohkubo, T. and Imai, Y. (2005b) The radial augmentation index: Determinants and association with left ventricular hypertrophy. *Am J Hypertens* 18: 14A (Abstract).

Hashimoto, J., Watabe, D., Hatanaka, R., Hanasawa, T., Metoki, H., Asayama, K. *et al.* (2006) Enhanced late-systolic blood pressure augmentation in hypertensive patients with left ventricular hypertrophy. *Am J Hypertens* 19: 27–32.

Hashimoto, J., Imai, Y. and O'Rourke, M.F. (2007) Indices of pulse wave analysis are better predictors of left ventricular mass reduction than cuff pressure. *Am J Hypertens* 20: 378–384.

Hashimoto, J., Nichols, W.W., O'Rourke, M.F. and Imai, Y. (2008a) Association between wasted pressure effort and left ventricular hypertrophy in hypertension: Influence of arterial wave reflection. *Am J Hypertens* 21: 329–333.

Hashimoto, J., Westerhof, B.E., Westerhof, N., Imai, Y. and O'Rourke, M.F. (2008b) Different role of wave reflection magnitude and timing on left ventricular mass reduction during antihypertensive treatment. *J Hypertens* 26: 1017–1024.

Hashimoto, J., Aikawa, T. and Imai, Y. (2008c) Large artery stiffening as a link between cerebral lacunar infarction and renal albuminuria. *Am J Hypertens* 21: 1304–1309.

Hashimoto, J. and O'Rourke, M.F. (2008) Is arterial stiffness better than blood pressure in predicting cardiovascular risk? *Curr Cardiovasc Risk Rep* 2: 113–140.

Hashimoto, J. and O'Rourke, M.F. (2009) Basic concepts and regulation of aortic function, In: Boudoulas, H. and Stefanadis, C. (eds). *The aorta: Structure, function, dysfunction, and diseases*, Informa Healthcare: London.

Hatanaka, R., Hashimoto, J., Watabe, D., Kondo, T., Hanazawa, T., Ohba, H. *et al.* (2006) Association of brachial-ankle pulse wave velocity with silent cerebrovascular disease. *J Hypertens* 24(suppl 6): 120 (Abstract).

Heijden-Spek, J.J., Staessen, J.A., Fagard, R.H., Hoeks, A.P., Struijker Boudier, H.A. and Van Bortel, L.M. (2000) Effect of age on brachial artery wall properties differs from the aorta and is gender dependent: A population study. *Hypertension* 35: 637–642.

Hirata, K., Yaginuma, T., O'Rourke, M.F. and Kawakami, M. (2006) Age-related change in the carotid artery flow and pressure pulses: implication to cerebral microvascular disease. *Stroke* 92: 1616–1622.

Ho, K. (1982) Effects of ageing on arterial distensibility and left ventricular load in an Australian population. BSc (Med) thesis, University of New South Wales, Australia.

Hoeks, A.P., Brands, P.J., Smeets, F.A. and Reneman, R.S. (1990) Assessment of the distensibility of superficial arteries. *Ultrasound Med Biol* 16: 121–128.

Ishikawa, T., Hashimoto, J., Watabe, D., Kondo, T., Hanazawa, T., Ohba, H. *et al.* (2008) Association of microalbuminuria with brachial-ankle pulse-wave velocity. *Am J Hypertens* 21: 413–418.

Ito, S., Nagasawa, T., Abe, M. and Mori, T. (2009) Strain vessel hypothesis: a view point for linkage of albuminuria and cerebro-cardiovascular risk. *Hypertens Res* 32: 115–121.

Jankowski, P., Kawecka-Jaszcz, K., Czarnecka, D., Brzozowska-Kiszka, M., Styczkiewicz, K., Loster, M. *et al.* (2008) Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. *Hypertension* 51: 848–855.

Karamanoglu, M., O'Rourke, M.F., Avolio, A.P. and Kelly, R.P. (1993) An analysis of the relationship between central and peripheral upper limb pressure waves in men. *Eur Heart J* 14: 160–167.

Kass, D.A., Shapiro, E.P., Kawaguchi, M., Capriotti, A.R., Scuteri, A., deGroof, R.C. *et al.* (2001) Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. *Circulation* 104: 1464–1470.

Kelly, R., Hayward, C., Avolio, A. and O'Rourke, M.F. (1989a) Noninvasive determination of age-related changes in the human arterial pulse. *Circulation* 80: 1652–1659.

Kelly, R.P., Hayward, C.S., Ganis, J., Daley, J.M., Avolio, A.P. and O'Rourke, M.F. (1989b) Non-invasive registration of the arterial pulse waveform using high fidelity applanation tonometry. *J Vasc Med Biol* 1: 142–149.

Kelly, R.P., Millasseau, S.C., Ritter, J.M. and Chowienczyk, R.P.J. (2001) Vasoactive drugs influence aortic augmentation index independently of pulse-wave velocity in healthy men. *Hypertension* 37: 1429–1433.

Lakatta, E.G. and Levy, D. (2003) Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: Aging arteries: A "set-up" for vascular disease. *Circulation* 107: 139–146.

Laurent, S., Caviezel, B., Beck, L., Girerd, X., Billaud, E., Boutouyrie, P. *et al.* (1994) Carotid artery distensibility and distending pressure in hypertensive humans. *Hypertension* 23: 878–883.

Laurent, S., Kingwell, B., Bank, A., Weber, M. and Struijker Boudier, H. (2002) Clinical applications of arterial stiffeness: therapeutics and pharmacology. *Am J Hypertens* 15: 453–458.

Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D. *et al.* (2006) Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 27: 2588–2608.

Lewington, S., Clarke, R., Qizilbash, N., Peto, R. and Collins, R. (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 360: 1903–1913.

Liao, D., Arnett, D.K., Tyroler, H.A., Riley, W.A., Chambless, L.E., Szklo, M. *et al.* (1999) Arterial stiffness and the development of hypertension: the ARIC study. *Hypertension* 34: 201–206.

London, G., Guerin, A., Pannier, B., Marchais, S., Benetos, A. and Safar, M. (1992) Increased systolic pressure in chronic uremia. Role of arterial wave reflections. *Hypertension* 20: 10–19.

McDonald, D.A. and Taylor, M.G. (1953) The hemodynamics of the arterial circulation. *Prog Biophys Chem* 9: 107–173.

McEniery, C.M., Yasmin, Hall, I.R., Qasem, A., Wilkinson, I.B. and Cockcroft, J.R. (2005) Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* 46: 1753–1760.

Michelson, G., Harazny, J., Schmieder, R.E., Berendes, R., Fiermann, T. and Warntges, S. (2007) Fourier analysis of the envelop of the ophthalmic artery blood flow velocity: Age- and blood-related impact. *Hypertension* 50: 964–969.

Millasseau, S.C., Guigui, F.G., Kelly, R.P., Prasad, K., Cockcroft, J.R., Ritter, J.M. *et al.* (2000) Noninvasive assessment of the digital volume pulse: Comparison with the peripheral pressure pulse. *Hypertension* 36: 952–956.

Mitchell, G.F., Isso, J.L., Lacourciere, Y., Ouellet, J.P., Neutel, J., Oian, C. *et al.* (2002) Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension. *Circulation* 105: 2955–2961.

Mitchell, G.F., Lacourciere, Y., Ouellet, J.P., Izzo, J.L., Neutel, J., Kersin, L.J. *et al.* (2003) Determinants of elevated pulse pressure in middle-aged and older subjects with uncomplicated systolic hypertension: the role of proximal aortic diameter and the aortic pressure-flow relationship. *Circulation* 108: 1592–1598.

Mitchell, G.F., Parise, H., Benjamin, E.J., Larson, M.G., Keyes, M.J., Vita., J, A. *et al.* (2004) Changes in arterial stiffness and wave refection with advancing age in healthy men and women: the Framingham Heart study. *Hypertension* 43: 1239–1245.

Mitchell, G.F. (2006) Triangulating the peaks of arterial pressure. *Hypertension* 48: 543–545.

Mitchell, G.F., Conlin, P.R., Dunlap, M.E., Lacourciere, Y., Arnold, J.M.O., Ogilvie, R.I. *et al.* (2008) Aortic diameter, wall stiffness, and wave reflection in systolic hypertension. *Hypertension* 51: 105–111.

Nagai, Y., Metter, E.J., Earley, C.J., Kemper, M.K., Becker, L.C., Lakatta, E.G. *et al.* (1998) Increased carotid artery intima-media thickness in asymptomatic older subjects with exercise-induced myocardial ischemia. *Circulation* 98: 1504–1509.

Najjar, S.S., Scuteri, A. and Lakatta, E.G. (2005) Arterial aging: is it an immutable cardiovascular risk factor? *Hypertension* 46: 454–462.

Nichols, W.W. (2005) Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. *Am J Hypertens* 18: 3S–10S.

Nichols, W.W. and O'Rourke, M.F.(2005) *McDonald's blood flow in arteries: Theoretical, experimental and clinical principles*, 5th edn, Hodder Arnold: London.

O'Rourke, M.F. and Taylor, M.G. (1966) Vascular impedance of the femoral bed. *Circ Res* 18: 126–139.

O'Rourke, M.F. and Safar, M.E. (2005) Relationship between aortic stiffening and microvascular disease in brain and kidney: Cause and logic therapy. *Hypertension* 46: 200–204.

O'Rourke, M.F. and Hashimoto, J. (2006) Mechanical factors in arterial aging: A clinical perspective. *J Am Coll Cardiol* 50: 1–13.

O'Rourke, M.F. and Hashimoto, J. (2008) Arterial stiffness: A modifiable cardiovascular risk factor? *J Cardiopulm Rehabil Prev* 28: 225–237.

Pauca, A.L., O'Rourke, M.F. and Kon, N.D. (2001) Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension* 38: 932–937.

Ravera, M., Ratto, E., Vettoretti, S., Viazzi, F., Leoncini, G., Parodi, D. *et al.* (2002) Microalbuminuria and subclinical cerebrovascular damage in essential hypertension. *J Nephrol* 15: 519–524.

Redfield, M.M., Jacobsen, S.J., Borlaug, B.A., Rodeheffer, R.J. and Kass, D.A. (2005) *Circulation* 112: 2254–2262.

Rizzoni, D., Porteri, E., Boari, G.E., De Ciuceis, C., Sleiman, I., Muiesan, M.L. *et al.* (2003) Prognostic significance of small-artery structure in hypertension. *Circulation* 108: 2230–2235.

Roman, M.J., Devereux, R.B., Kizer, J.R., Lee, E.T., Galloway, J.M., Ali, T. *et al.* (2007) Central pressure more strongly relates to vascular disease and outcome than brachial pressure. *Hypertension* 50: 197–203.

Safar, M.E. (2004) Peripheral pulse pressure, large arteries, and microvessels. *Hypertension* 44: 121–122.

Schleider, J. (1918) Der Energieverbrauch in der Blutbahn. *Pflugers Archiv fur die gesamte Physiologie* 173: 172–223.

Shargorodsky, M., Hass, E., Boaz, M., Gavish, D., Zimlichman. and R. (2008) High dose treatment with angiotensin II receptro blocker in patients with hypertension: Differential effect of tissue protection versus blood pressure lowering. *Atherosclerosis* 197: 303–310.

Struijker Boudier, H.A.J., Cohuet, G.M.S., Bauman, M. and Safar, M.E. (2003) The heart, macrocirculation and microcirculation in hypertension: a unifying hypothesis. *J Hypertens* 21(supple 3): S19–S23.

Taddei, S., Virdis, A., Mattei, P., Ghiadoni, L., Fasolo, C.B., Sudano, I. *et al.* (1997) Hypertension causes premature aging of endothelial function in humans. *Hypertension* 29: 736–743.

Taddei, S., Virdis, A., Ghiadoni, L., Salvetti, G., Bernini, G., Magagna, A. *et al.* (2001) Age-related reduction of NO availability and oxidative stress in humans. *Hypertension* 38: 274–279.

Takazawa, K., Tanaka, N., Takeda, K., Kurosu, F. and Ibukiyama, C. (1995) Underestimation of vasodilator effects of nitroglycerin by upper limb blood pressure. *Hypertension* 26: 520–523.

Takazawa, K., Tanaka, N., Fujita, M., Matsuoka, O., Saiki, T., Aikawa, M. *et al.* (1998) Assessment of vasoactive agents and vascular aging by the second derivative of photoplethysmogram waveform. *Hypertension* 32: 365–370.

Tanaka, H., Dinenno, F.A., Monahan, K.D., DeSouza, C.A. and Seals, D.R. (2001) Carotid artery wall hypertrophy with age is related to local systolic blood pressure in healthy men. *Arterioscler Thromb Vasc Biol* 21: 82–87.

Tomiyama, H., Yamashina, A., Arai, T., Hirose, K., Koji, Y., Chikamori, T. *et al.* (2003) Influence of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement – a survey of 12517 subjects. *Atherosclerosis* 166: 303–309.

Tropeano, A., Boutouyrie, P., Pannier, B., Joannides, R., Balkestein, E., Katsahian, S. *et al.* (2006) Brachial pressure-independent reduction in carotid stiffness after long-term angiotensin-converting enzyme inhibition in diabetic hypertensives. *Hypertension* 48: 80–86.

Vasan, R.S., Larson, M.G. and Levy, D. (1995) Determinants of echocardiographic aortic root size. The Framingham Heart Study. *Circulation* 91: 734–740.

Vicaut, E. (1999) Microcirculation and arterial hypertension. *Drugs* 58: 1–10.

Virmani, R., Avolio, A.P., Mergner, W.J., Robinowitz, M., Herderick, E.E., Cornhill, J.F. *et al.* (1991) Effect of aging on aortic morphology in populations with high and low prevalence of hypertension and atherosclerosis: comparison between occidental and Chinese communities. *Am J Pathol* 139: 1119–1129.

Vlachopoulos, C., Hirata, K. and O'Rourke, M.F. (2001) Pressure altering agents affect central aortic pressures more than is apparent from upper limb measurements in hypertensive patients: The role of arterial wave reflections. *Hypertension* 38: 1456–1460.

Wada, M., Nagasawa, H., Kuriata, K., Koyama, S., Arakawa, S., Kawanami, T. *et al.* (2007) Microalbuminuria is a risk factor for cerebral small vessel disease in community-based elderly subjects. *J Neurol Sci* 255: 27–34.

Wang, M., Zhang, J., Jiang, L.Q., Spinetti, G., Pintus, G., Monticone, R. *et al.* (2007) Proinflammatory profile within the grossly normal aged human aortic wall. *Hypertension* 50: 219–227.

Watabe, D., Hashimoto, J., Hatanaka, R., Hanazawa, T., Ohba, H., Ohkubo, T. *et al.* (2006) Electrocardiographic left ventricular hypertrophy and arterial stiffness: The Ohasama study. *Am J Hypertens* 19: 1199–1205.

Westerhof, B.E., Guerlen, I., Westerhof, N., Karemaker, J.M. and Avolio, A. (2006) Quantification of wave reflection in the human aorta from pressure alone: A proof of principle. *Hypertension* 48: 595–601.

Westerhof, N. and O'Rourke, M.F. (1995) Haemodynamic basis for the development of left ventricular failure in systolic hypertension and for its logical therapy. *J Hypertens* 13: 943–952.

Wilkinson, I.B., Franklin, S.S., Hall, I.R., Tyrrell, S. and Cockcroft, J.R. (2001) Pressure amplification explains why pulse pressure is unrelated to risk in young subjects. *Hypertension* 38: 1461–1466.

Williams, B., Lacy, P.S., Thom, S.M., Cruickshank, K., Stanton, A., Collier, D. *et al.* (2006) Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 113: 1213–1225.

Wojciechowska, W., Staessen, J.A., Nawrot, T., Cwynar, M., Seidlerova, J., Stolarz, K. *et al.* (2006) Reference values in white Europeans for the arterial pulse wave recorded by means of the SphygmoCor device. *Hypertens Res* 29: 475–483.

Womersley, J.R. (1957) Oscillatory flow in arteries: the constrained elastic tube as a model of arterial flow and pulse transmission. *Phys Med Biol* 2: 178–187.

Yamashina, A., Tomiyama, H., Takeda, K., Tsuda, H., Arai, T., Hirose, K. *et al.* (2002) Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 25: 359–364.