Arterial aging—hemodynamic changes and therapeutic options

Michel E. Safar

Abstract | Arterial aging can be attributed to two different pathophysiological changes—increase in arterial stiffness and disturbed wave reflections. The capacity of the aorta to absorb the force exerted by the left ventricular ejection and dampen pulsatile flow becomes diminished with advancing age, owing to the progressive hardening of the arterial wall. These changes contribute to increase blood pressure, mainly systolic blood pressure and pulse pressure, which can trigger cardiovascular events. Understanding the pulsatile arterial hemodynamics that elevate cardiovascular risk has led to the use of pharmacological therapies, which prevent arterial stiffness and reduce wave reflections, and improve cardiovascular morbidity and mortality. Antifibrotic agents, such as those that block the renin–angiotensin–aldosterone pathway, are often given in association with diuretics, calcium-channel blockers, or both, but not with standard β-blockers. Consistent reductions in cardiovascular outcomes obtained using these agents can be predicted through noninvasive measurements of central systolic blood pressure and pulse pressure.

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Introduction

Over the past 50 years, one of the major findings from studies of cardiovascular disease has been the proven effectiveness of antihypertensive therapy.[1] These treatments are beneficial for the prevention of stroke, heart failure, renal insufficiency and, to a lesser extent, coronary artery disease (CAD).[2,3] In clinical trials of hypertension, diastolic blood pressure (DBP) under drug treatment is usually ≤90 mmHg, whereas systolic blood pressure (SBP) often remains elevated (≥140 mmHg).[4] Increased pulse pressure (PP)—the difference between SBP and DBP—is, therefore, observed in approximately 30% of treated patients.[3] Isolated systolic hypertension, defined as raised SBP but normal DBP, is the predominant form of hypertension in elderly people (≥65 years); systolic–diastolic hypertension is not as common in this population, as DBP stabilizes or even declines with advancing age. Progressive arterial stiffness, as a result of structural and functional changes within the vessel wall, is a feature of aging and may precede the onset of hypertension. A more thorough understanding of the changes in pulsatile arterial hemodynamics that occur with advancing age is necessary to develop and provide the most appropriate treatment. This Review describes the hemodynamic changes that arise as a result of the arterial aging process. Therapeutic aspects, especially those relating to blockade of the renin–angiotensin–aldosterone system, are also discussed.

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Pathophysiological vascular remodeling

Aging is accompanied by changes in vascular structure and function, especially in the large arteries, which affect the heart and other organs. The arterial wall is composed of various cell populations that form the intima (endothelial cells and elastic lamina) and the media (smooth muscle and elastic tissue). These cells adapt to the continuous stimuli and mechanical forces to which they are exposed, and respond to injury, atherogenic factors, and long-term hemodynamic conditions. To maintain basal levels of tensile stress (Laplace's law), progressive thickening of the vessel wall occurs as a result of the proliferation and migration of vascular smooth

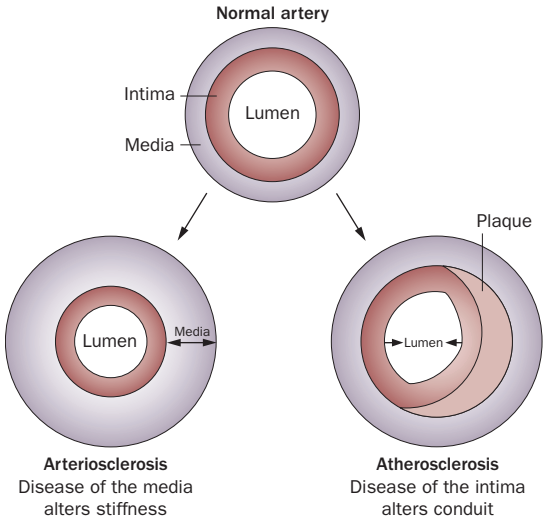

Figure 1 | Changes in arterial diameter in patients with arteriosclerosis or atherosclerosis. Individuals with arteriosclerosis are affected by changes in the thickness of the blood vessel wall owing to smooth muscle proliferation, which alters the size of the lumen and stiffness of the artery, and leads to impaired blood circulation. Atherosclerosis is characterized by arterial stenosis, with presence of plaques that restrict blood flow through the lumen.

Key points

- Changes in the vasculature occur with advancing age, especially in the large arteries, which affect the function of the heart and other organs
- Arterial stiffness and increased pulse wave velocity are important predictors of cardiovascular disease, particularly in the elderly
- Systolic hypertension is the most common type of hypertension in the elderly, and occurs as a result of age-related structural and functional changes in the vasculature
- Antifibrotic agents, mainly those that block the renin–angiotensin–aldosterone system, are the primary basis of treatment to prevent arterial stiffening and lower blood pressure
- The use of diuretics, calcium-channel inhibitors, or both may also be required to reduce cardiovascular outcomes, but standard β-blockers should be avoided

muscle cells.[5,6] Experimental and clinical data show that increases in blood flow induce proportional increases in the size of the lumen, whereas diminished flow leads to reduction of the vascular mass.[7] The endothelium is important for normal vascular adaptation to chronic changes in blood flow and blood pressure.[8,9] Endothelial dysfunction is characteristic of arterial aging, frequently triggered by nitric oxide deficiency and/or development of oxidative stress.[3,7,10]

Vascular hypertrophy of the arterioles is common in patients with hypertension, where the medial layer is thickened and the lumen is reduced (arteriosclerosis). Arterioles are sites of vascular resistance and the origin of wave reflections, which both increase in hypertensive patients.[7,11–14] Capillary rarefaction is also frequently associated with remodeling, which leads to increased peripheral resistance. The prevalence of atherosclerosis is also linked to vascular remodeling and aging; plaque formation frequently occurs in areas of disturbed flow or high pressure, which further increases the risk of cardiovascular events (Figure 1).

Early markers of arterial aging

Increased PP is a typical modification of blood pressure in the elderly. SBP increases progressively with age, whereas DBP usually only increases until 55 years of age and then declines, even without drug treatment.[15] In the absence of disturbed ventricular ejection, an increase in PP indicates a progressive increase in arterial stiffness.[2] In a longitudinal study,[16] 4,592 men and women aged between 30 and 65 years were followed-up to determine the rates of change of SBP and DBP with age (Figure 2). Mean values of SBP, DBP, and other cardiometabolic risk factors were measured every 3 years over a 9-year period. Whereas mean values of SBP and DBP increased linearly with age (Figure 2a), their rates of change were divergent; the rate of change increased linearly for SBP, but DBP began to decline from as early as 45 years of age (Figure 2b). This finding suggests that vascular aging is an active process that starts before the age of 50 years, and indicates the early stages of cardiovascular damage.[16] In women, menopause has an effect on PP and may contribute to an accelerated aging process.[17,18]

Importantly, there are two different components of the blood-pressure curve: a steady component (mean arterial pressure [MAP]), and a pulsatile component (PP).[2] MAP is determined by cardiac output and vascular resistance, and refers to the status of the microcirculation, whereas PP is influenced by stroke volume, arterial stiffness, and wave reflections and relates to the macrocirculation. Both arterial stiffness and wave reflections influence the buffering function of large arteries (Windkessel effect), a process that normally provides a continuous blood flow when the heart is between contractions in order to supply oxygen to peripheral tissues. Arteries lose this function as they stiffen, so the heart has to work harder and the coronary flow is reduced, potentially leading to ischemia. PP increases markedly with advancing age and is an independent predictor of coronary risk, whereas MAP is usually unchanged and predicts the overall cardiovascular risk (kidney, heart, and brain).[19,20]

PWV and PP amplification

Following ventricular contraction, the pressure generated by the heart travels along the aorta as a wave. The pulse wave velocity (PWV) is the time taken by the pressure wave to travel between two different sites in the arterial tree. Because pulse waves travel faster in stiffer arteries, PWV is considered to be the best measure of arterial stiffness. The resting PWV in the aorta is approximately 10 m/s in a person aged 60–65 years and continues to increase with advancing age. Aortic PWV is a strong and independent predictor of cardiovascular risk, particularly in the elderly.[21,22]

Blood pressure measurements taken simultaneously at different points along the aorta demonstrate that the pressure waveform changes as it travels along this vessel. Whereas SBP rises with distance from the heart, DBP

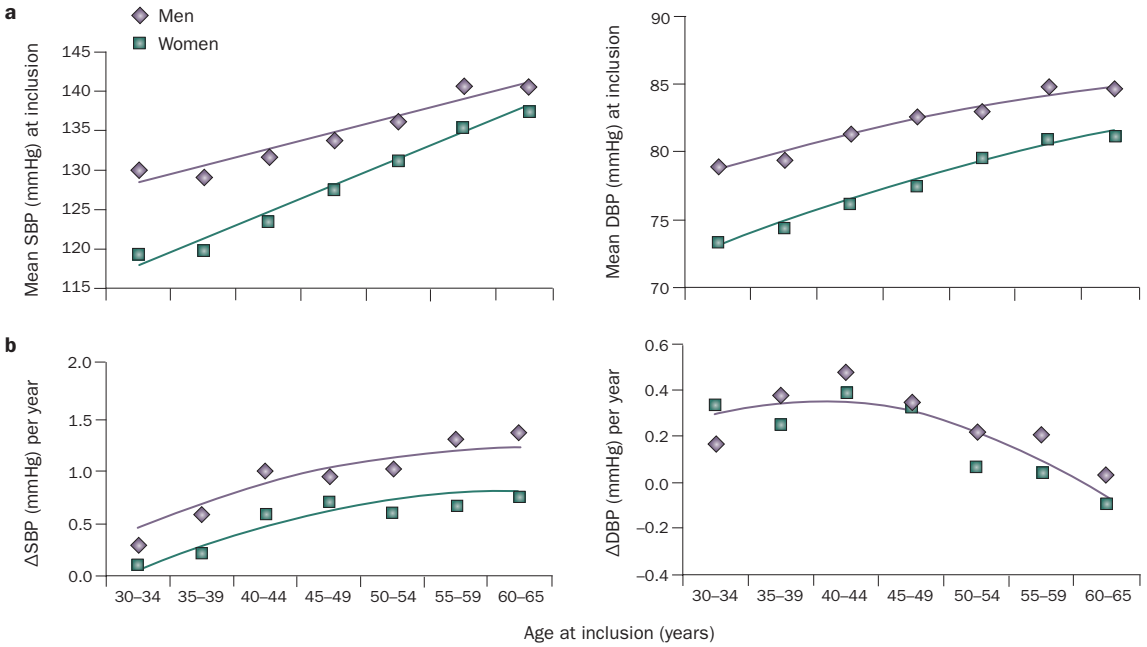

Figure 2 | Relationship between age and blood pressure from the DESIR study.[16] **a** | Mean values of SBP and DBP by age and sex; data points indicate observed mean SBP (left) and DBP (right) by age, and the lines are best-fit linear regression lines. **b** | Mean change (Δ) per year in SBP (left) and DBP (right) by age and sex; data points indicate observed mean changes per year by age, and the lines are best-fit linear regression lines. Both SBP and DBP increase with age, more rapidly in women than in men, but ΔDBP is usually markedly reduced from as early as 45 years. Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure. Permission obtained from Wolters Kluwer/Lippincott, Williams & Wilkins © Safar, M. E. *et al.* The Data from an Epidemiologic Study on the Insulin Resistance Syndrome Study: the change and rate of change of the age-blood pressure relationship. *J. Hypertens.* **26**(10), 1903–1911.

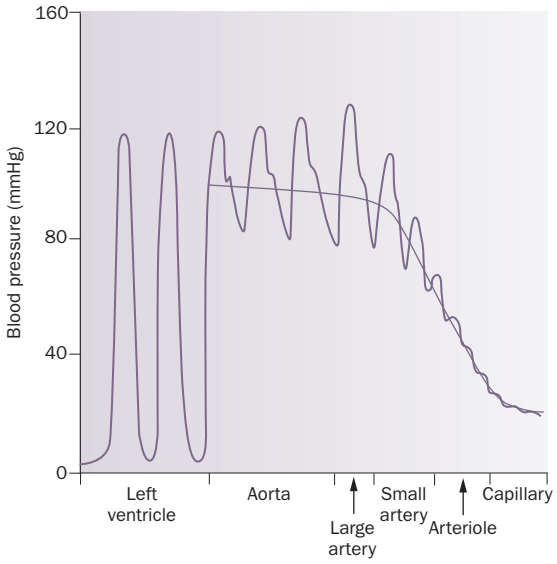

Figure 3 | Schematic representation of blood pressure in different topographies of the arterial tree. Pulsatility is highest in the large arteries, but pulsatile flow begins to disappear in the small arteries and arterioles, and is almost constant at the level of the capillary network.

and MAP fall slightly (2–4 mmHg) over the same course along the aortic trajectory. Thus, the amplitude of pressure oscillations between systole and diastole, represented by central PP, nearly doubles.[3] The amplification of SBP and PP is approximately 14 mmHg between the thoracic aortic root and the brachial artery towards the third ramifications of arterial branches. PP amplification in central arteries protects the heart against an increase in vascular afterload, but this protection is attenuated with age, and disappearance of PP amplification is a predictor of cardiovascular risk.[23] The amplitude of both PP and MAP fall in the microcirculation, where nonpulsatile, steady flow is nearly achieved (Figure 3).

Changes in wave reflections

As the incident wave moves from the heart through the highly conductive arteries, it encounters an impedance mismatch at the junction of the artery and smaller high-resistance arterioles, which blocks its entry and causes a reflection that travels back towards the heart (Box 1). The shape of every observed pulse wave results from the summation of the incident (forward-traveling) and reflected (backward-traveling) pressure wave (Figure 4).[24] Reflected waves may arise from any bifurcation of the arterial or arteriolar wall, but are mainly issued from high-resistance vessels in the periphery.[3,17] Pulse wave propagation and reflection vary considerably according to age. Elasticity of the central arteries is greatest in young adults, which equates to low PWV. The summation of the incident arterial pressure wave and the observed reflected wave results in progressive PP amplification, so that SBP is higher in the brachial artery than in the ascending aorta. Because PWV is low in the thoracic aorta, the reflected waves

return during diastole, thereby maintaining DBP and boosting coronary perfusion. Optimal arterial function is thus obtained.

The development of arterial stiffness and disturbed wave reflections abolish the differences between central and peripheral PP by the age of 50–60 years. This process has major consequences on ventricular load and coronary perfusion. The increased PWV means that the reflected waves return to the aortic root during late systole when the heart is ejecting blood. The reflected waves summate with the forward-traveling wave and augment the pressure in the aorta, which increases central SBP and ventricular load. This supplementary increase in SBP, expressed as the augmentation index (Aix, Figure 4), is an independent predictor of cardiovascular risk.[25] In elderly individuals with isolated systolic hypertension, aortic SBP can be elevated by 30–40 mmHg as a result of the early return and amplitude of wave reflection. Furthermore, because the backward pressure returns in systole and not in diastole as a consequence of increased PWV, DBP and coronary blood flow are usually reduced, a situation that favors coronary ischemia independent of atherosclerosis. Reduced heart rate in the elderly shifts wave reflection from diastole to systole, thus increasing central SBP (Figure 5). Insulin resistance may also change wave reflection and central SBP.[26] Blockade of the renin–angiotensin–aldosterone system with angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), or by calcium-channel blockade, as well as insulin administration, may reduce wave reflection and central SBP.[26,27]

Central versus brachial PP

Aortic PP is a better predictor of cardiovascular events than brachial PP as it more accurately represents the load imposed on coronary and cerebral arteries.[2,3] Similarly, aortic but not brachial pulsatility is independently associated with CAD in patients before or after angioplasty, as assessed by coronary angiography.[28–30] In one of the first studies to determine the prognostic importance of central blood pressure-derived indices, Jankowski *et al.* followed-up 409 patients for 4.5 years and showed that a 10 mmHg increase in aortic PP was associated with a corresponding 13% increase in cardiovascular events.[31] Central wave reflections were independent predictors of CAD in patients with atherosclerosis.[31,32] In patients with end-stage renal disease, aortic PWV, carotid wave reflections, and/or central PP were independent predictors of cardiovascular mortality.[3,33] Central PP was also an independent predictor of cardiovascular and overall mortality in patients with end-stage renal disease and in elderly individuals with essential hypertension.[32,34,35] Collectively, these findings suggest that central PP is superior to brachial PP for prediction of coronary risk, and indicate that serial central blood pressure measurements are required during long-term antihypertensive drug therapy to predict cardiovascular complications, particularly in the elderly.[23,32] Noninvasive assessment of hemodynamics is possible using the SphygmoCor® system (AtCor Medical, West Ryde, Australia), which is currently the most widely used family of devices to determine central blood pressure.[2]

Box 1 | Pressure wave travel and reflections in the aorta and large arteries[24]

Imagine the pressure and flow waves as they travel along the aorta and after they are reflected in a hypothetical vessel that is closed at the end. Both pressure and flow are reflected, and the magnitude of the reflection is the same for both. However, in this example of a closed vessel, the pressure wave is reflected 'upright' whereas the flow wave is reflected 'upside down', that is, inversely with respect to pressure. In a tube without a closed end, pressure and flow are also both partially reflected, but flow is always inverted with respect to pressure. The reflected waves return to the heart with the same velocity as the forward waves. The summation of forward and backward waves produces the observed wave. If no reflections occur, the measured pressure and flow waves are similar in wave shape. Thus, reflections are the reason why pressure and flow differ in shape.

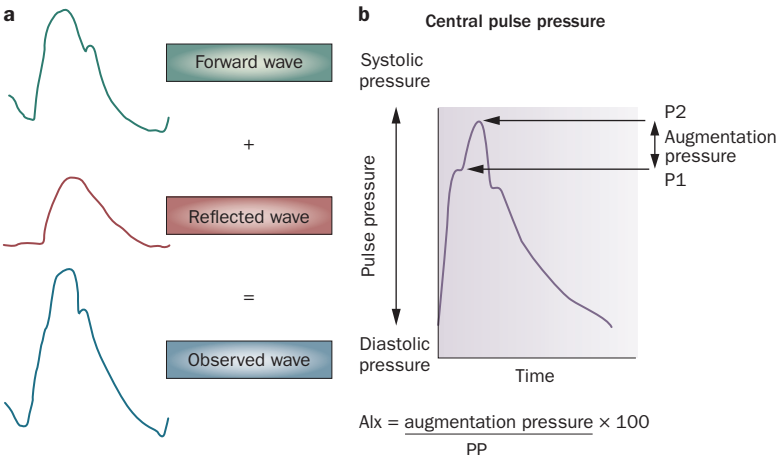

Figure 4 | Pressure wave traveling from the heart to the periphery. **a** | The pressure wave involves three parts: propagation, reflection, and return of reflected wave. The observed wave is the summation of the forward-traveling and backward-traveling wave. **b** | The augmentation pressure represents the supplementary increase in SBP owing to the wave reflections that return during the systole phase, which increase as a result of vascular aging. Aix is calculated as the augmentation pressure divided by PP and multiplied by 100 (expressed as a percentage). Abbreviations: Aix, augmentation index; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

Treatment for arterial aging

Antihypertensive therapy undoubtedly reduces morbidity and mortality in the elderly (Figure 6). Treatment is aimed at preventing arterial stiffness, and reducing wave reflections and SBP. However, treatment does not differentiate between isolated systolic and systolic–diastolic hypertension, although DBP is normal or low in individuals with isolated systolic hypertension. Also, CAD is poorly prevented by treatment. A combination of drugs should be used to enhance the prevention of arterial stiffness and reduction of wave reflection. If there is no specific indication for standard β-blockers, it seems relevant to propose diuretics and/or calcium-channel blockers, mainly in association with angiotensin blockade.

Blockade of angiotensin II is associated with reductions in vascular resistance and MAP.[2,3] By contrast, the effects of this therapy on PWV and central and peripheral PP were poorly investigated up until the past two decades.

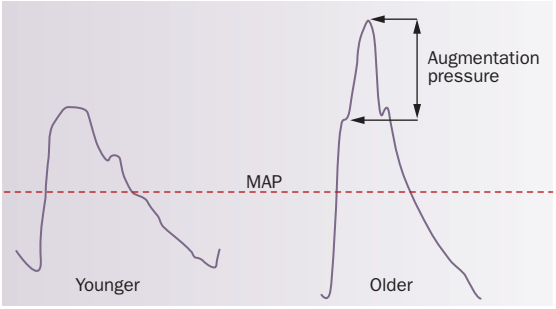

Figure 5 | Representative BP curves for young and old individuals with the same MAP. The shape of the BP curve in elderly individuals (>65 years of age) usually has lower DBP and raised SBP owing to vascular aging. Note the increase in augmentation pressure with advancing age, which is a manifestation of wave reflections returning during late systole. Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

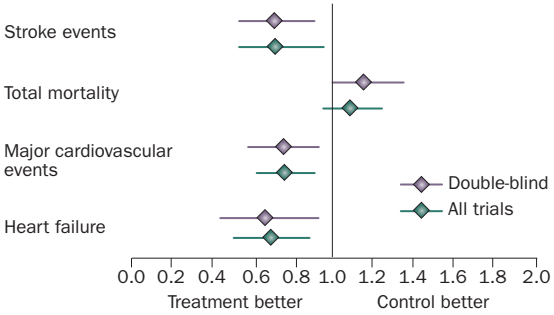

Figure 6 | Meta-analysis of the effects of antihypertensive therapy in patients >80 years.[56] Data were collected from 1,670 participants >80 years of age in randomized, controlled trials of antihypertensive drugs. Rates of cardiovascular events, stroke, and heart failure were significantly decreased. However, there was no treatment benefit for cardiovascular death. Reprinted from *Lancet* **353**, Gueyffier, F. *et al.* Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. 793–796 © 1999, with permission from Elsevier.

Angiotensin II inhibitors, aldosterone antagonists and, to a lesser extent, calcium-channel blockers, reduce arterial stiffness independently of MAP,[36] whereas diuretics and β-blockers have little or no effect on this parameter. Studies in animal models and in humans indicate that angiotensin II blockade is associated with reverse remodeling of both small and large arteries via mechanisms that include anti-inflammatory and antifibrotic effects, as well as a decrease in arterial attachments that link the integrin α5β1 to its ligand fibronectin.[27] In vascular cells, focal adhesions are composed of cytoskeletal proteins that are linked to the extracellular matrix (ECM) by integrin receptors. Integrins interact with components of the ECM, including fibronectin (ligand for α5β1 and αvβ3), vitronectin (ligand for αvβ3), and laminin (ligand for α6β1).[3,27] These macromolecular complexes are major sites of anchorage through which mechanical force is transmitted.[37,38] Regression of arteriolar hypertrophy following drug treatment is characterized by diminution of vascular resistance and of reflection coefficients, thereby lowering SBP, PP and Aix.[11–13] This improvement occurs after approximately 1 year of treatment in hypertensive patients under angiotensin or calcium-channel blockade, but not under thiazide diuretics or standard β-blockers.[10,14]

Experimental studies of arterial aging

Using a murine model, Louis *et al.* showed that α1β1 integrin (receptor for collagen and laminin) was necessary for the development of arterial hypertrophy in response to angiotensin II.[39] When cyclic mechanical strain is applied to matrices containing various adhesion proteins, fibronectin produces one of the largest mitogenic responses in the vascular smooth muscle of rats.[40] The expression of fibronectin and its receptor are also increased in the aorta of spontaneously hypertensive rats.[40] This increase may denote an increased number of mechanical attachments between the ECM and collagen fibers within the arterial media, which promotes stiffness.[27,40] In animals, these changes have been studied primarily in situations involving normal or increased sodium intake in the presence of angiotensin II stimulation or blockade.[41,42] Angiotensin II and sodium intake are major determinants of elevated fibronectin in animal models. Indeed, in spontaneously hypertensive rats receiving normal sodium intake, ACE inhibition or blockade of the angiotensin I receptor reduced carotid MAP, PP, aortic collagen content, aortic fibronectin, and α5β1 integrin expression, and demonstrated a reduction in binding between fibronectin and α5β1, as well as an increased isobaric arterial distensibility.[41,42] By contrast, when spontaneously hypertensive rats were given a high-sodium diet, the carotid PP and isobaric distensibility remained unchanged following ARB treatment, although MAP was reduced. Aortic fibronectin and the attachment molecules remained enhanced. Similar observations have been made in Sprague-Dawley rats during chronic aldosterone infusion and a high-sodium diet.[13] Increased fibronectin and arterial stiffness, as well as aldosterone-induced proinflammatory factors were completely reversed by the selective aldosterone antagonist eplerenone.[43] With a normal-sodium diet, angiotensin II or aldosterone blockade reduced MAP and PP, and decreased collagen accumulation, fibronectin and its receptor. On a high-sodium diet, MAP but not central PP, was reduced by angiotensin II blockade in association with collagen accumulation, increased fibronectin, and increased arterial stiffness.[43] These findings suggest a prominent role for integrins in the mechanotransduction of blood pressure in rodents after prolonged administration of angiotensin II or aldosterone.

Clinical studies of arterial aging

In patients with hypertension receiving angiotensin II inhibitors, PWV is decreased independently of MAP, central wave reflections are also attenuated, and SBP and PP are decreased.[11] Angiotensin II blockade improves, or even normalizes, the wall thickness of resistance arteries and at the same time, reduces pressure wave reflections, suggesting a cause-and-effect relationship between the two factors.[11] Both ACE inhibitors and ARBs are able

to selectively reduce SBP and PP by decreasing arterial stiffness and wave reflections.[44–46]

The REASON study

In REASON (Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study),[11,47] the interactions between central PP, arterial stiffness, and wave reflections with angiotensin blockade and end organ damage (cardiac mass) were investigated in middle-aged, hypertensive individuals. Over a 1-year period, patients were randomly assigned to receive either the ACE inhibitor perindopril combined with low-dose indapamide ($n = 235$), or only the β-blocker atenolol ($n = 234$). Reduction in DBP and MAP were the same for both groups, but perindopril/indapamide significantly lowered SBP and PP compared with atenolol ($P < 0.001$). The reduction was more pronounced on central than on peripheral arteries (Figure 7). The two regimens lowered PWV and MAP to the same extent. By contrast, only perindopril/indapamide reduced central PP and Aix ($P < 0.001$).[11,47] Furthermore, a substudy showed that perindopril/indapamide significantly decreased cardiac hypertrophy compared with atenolol, as a consequence of the decrease in Aix ($P < 0.001$).[47] The lowering of SBP under drug treatment was adequately predicted by baseline enhanced PWV.[48] The small SBP reduction under atenolol was owing to maintained wave reflections and arteriolar hypertrophy. For perinopril/indapamide, regression of arteriolar hypertrophy was the first determinant factor after 1-year treatment, followed by the reduction of reflection coefficients.[11] ACE inhibitors are highly effective in angiotensin blockade, whereas standard β-blockers generally have a negative or no effect.[47,49]

Angiotensin II blockade with diuretics

The first trial to demonstrate the predictive value of aortic stiffness in hypertensive individuals was carried out in patients with end-stage renal disease.[50] The aim was to reduce cardiovascular morbidity and mortality through a therapeutic regimen involving salt and water depletion by dialysis, diuretics, or both to achieve dry weight; patients were then randomly assigned to receive an ACE inhibitor or calcium-channel blocker. If the target blood pressure was not achieved, atenolol was prescribed. A combination of the ACE inhibitor and calcium-channel antagonist in association with the β-blocker was prescribed if target blood pressure was still not achieved. During follow-up (mean of 51 months), treatment-related MAP reduction was associated with a reduction in PWV, lowering cardiovascular risk. MAP, brachial PP, and aortic PWV were all reduced in those who survived the follow-up period. For patients who died from cardiovascular events, MAP had been reduced to the same extent as in those who survived, but PWV and brachial PP were not modified by drug treatment. Thus, survival of patients with end-stage renal disease was significantly better when aortic PWV was decreased as a result of blood pressure-lowering treatment ($P < 0.001$). After adjustment for all confounding factors, the risk ratio for all-cause mortality, and cardiovascular mortality in those with unchanged PWV was 2.59 (95% CI 1.51–4.43) and 2.35 (95% CI 1.23–4.51), respectively. The prognostic value of PWV insensitivity to reduction in blood pressure on survival was independent of age, changes in blood pressure, and blood-chemistry abnormalities. In this trial, prolonged survival was more closely associated with the use of the ACE inhibitor than the other drugs, or with the number of drugs used. The use of the β-blocker and/or the calcium-channel blocker had no direct impact on patient outcomes.[50]

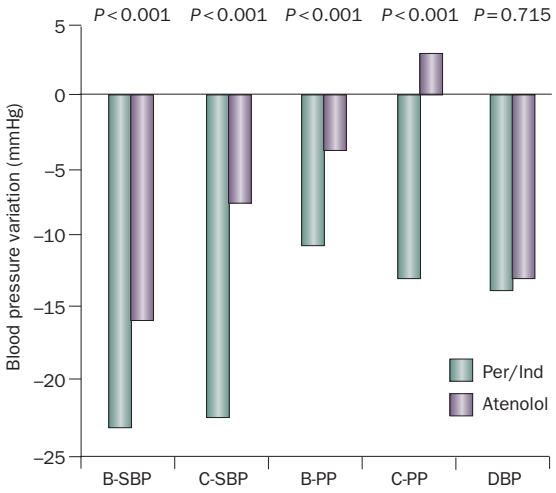

Figure 7 | Central and brachial blood pressure variation in the REASON study before and after 1 year of treatment. Patients were treated either with perindopril/indapamide or atenolol to compare their effects on central and brachial SBP.[57] DBP reduction was similar for the two drugs, but the reduction in SBP and PP was more pronounced following perindopril/indapamide treatment. Abbreviations: B-PP, brachial pulse pressure; B-SBP, brachial systolic blood pressure; C-PP, carotid pulse pressure; C-SBP, carotid systolic pulse pressure; DBP, diastolic blood pressure; Ind, indapamide; Per, perindopril; SBP, systolic blood pressure.

The combination of perindopril with indapamide was evaluated in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron-Modified Release Controlled Evaluation) study.[51] This was a double-blind, placebo-controlled trial where the investigators randomly assigned 11,340 participants to standard or intensive glucose therapy. The mean follow-up was 4.3 years. Reduction in blood pressure was associated with decreases in overall and cardiovascular mortality. SBP and PP were the most effective determinants of the risk of major cardiovascular outcomes, whereas DBP was the least effective determinant. Notably, diabetes, but not blood pressure, was the selection criterion for patients enrolled in ADVANCE.[51] However, the predictive values of blood pressure were in agreement with those of REASON.[11,47]

Angiotensin II and calcium-channel blockade

The CAFE (Conduit Artery Functional Evaluation) study[52] included 2,073 individuals to investigate the effects of two blood pressure-lowering regimens on

central aortic pressure. Results showed that aortic PP, recorded noninvasively by radial tonometry and transfer functions, was an important determinant of clinical outcomes independent of age and other confounding factors. In agreement with REASON,[11,47] the CAFE study showed that treating patients with a regimen based on a β-blocker (atenolol) and a diuretic (bendroflumethiazide) compared with a regimen of a calcium-channel blocker (amlodipine) and an ACE inhibitor (perindopril), had similar effects on brachial SBP and PP, but different impacts on central aortic pressures. Central SBP and PP were significantly lower for the amlodipine/perindopril arm (95% CI 3.3–5.4, $P<0.0001$ and 95% CI 2.1–3.9, $P<0.0001$, respectively).[51] The results of CAFE demonstrated that brachial PP does not always reflect the effects of blood pressure-lowering treatments on central aortic pressures, and also suggested that changes in central pressure may be a better predictor of clinical outcomes than brachial pressure.

A comparison of the ARB olmesartan in combination with either a calcium-channel blocker or a diuretic was carried out in 207 hypertensive patients (mean age 68.4 years).[53] In this open-label, blinded end-point study, patients received olmesartan monotherapy for 12 weeks, followed by additional use of azelnidipine ($n=103$) or hydrochlorothiazide ($n=104$) for 24 weeks after randomization. Following adjustment for baseline covariates, the reduction in central SBP in the olmesartan/azelnidipine group was significantly greater than in the olmesartan/diuretic group ($P=0.039$). In addition, aortic PWV was significantly reduced in patients receiving the olmesartan/azelnidipine combination compared with patients receiving olmesartan/diuretic ($P<0.001$). The reduction in brachial ambulatory SBP was similar for both groups. In this study, Matsui *et al.* provided evidence on the mechanism of reduction of SBP and PP amplification by calcium-channel blockers, namely by reducing PWV and Aix.[53] Reduction in pressure wave reflections was an important mechanism of central SBP reduction by calcium-channel blockers and, although heart rate was decreased in the olmesartan/azelnidipine arm, Aix was also reduced as a result of the reduction of wave reflections from peripheral sites. Again, these results demonstrate that arterial stiffness and wave reflections are involved in the mechanism of central SBP and PP reduction.

Conclusions

Reducing PP, particularly central PP, may prevent arterial stiffness and decrease wave reflections in elderly patients with systolic hypertension. Most therapeutic protocols involve inhibition of the renin–angiotensin–aldosterone system, frequently in association with diuretics, calcium-channel blockers, or both. The basis of treatment is not only hormonal blockade, but also modification of mechanotransduction mechanisms, such as the interactions between integrin α5β1 and its ligand fibronectin. Several approaches to ameliorate arterial aging need to be examined further in the future. First, a high BMI is frequently associated with increased arterial stiffness; weight reduction may, therefore, lead to decreased arterial rigidity and reduced wave reflections.[54] Second, developing novel drugs that inhibit angiotensin II will be important in terms of reducing cardiovascular risk. For example, ACE 2 (a human homolog of ACE) converts angiotensin II into angiotensin-(1–7), which is a heptapeptide with vasodilatory and cardioprotective properties that may be beneficial for patients with hypertension.[55] These effects should be validated in clinical studies. Finally, assessment of pulsatile arterial hemodynamics, particularly central blood pressure, should be routine in the clinic as it is crucial for the early identification of patients with arterial aging.

Review criteria

This article is based on a search of the PubMed and MEDLINE databases for English language articles published between 1980 and 2010. Search terms included "vascular aging", "vascular elasticity", and "systolic hypertension in the elderly" in association with "epidemiology", "genetics", and "drug treatment". The references of identified articles were also searched for further papers.

1. Staessen, J. E., Li, Y., Thijs, L. & Wang, J. G. in *Handbook of Hypertension: Arterial Stiffness in Hypertension* Vol. 23 Ch. 29 (eds Safar, M. E. & O'Rourke, M. F.) 459–484 (Elsevier, Edinburgh, 2006).
2. Nichols, W. W. & O'Rourke, M. F. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*, 5th edn (Hodder Arnold, London, 2005).
3. Safar, M. E. & O'Rourke, M. F. (eds) *Handbook of Hypertension: Arterial Stiffness in Hypertension* Vol. 23 (Elsevier, Edinburgh, 2006).
4. Black, H. R. The paradigm has shifted, to systolic blood pressure. *Hypertension* **34**, 386–387 (1999).
5. Langille, B. L. Remodeling of developing and mature arteries: endothelium, smooth muscle, and matrix. *J. Cardiovasc. Pharmacol.* **21** (Suppl. 1), S11–S17 (1993).
6. Levy, B. I., Ambrosio, G., Pries, A. R. & Struijker-Boudier, H. A. Microcirculation in hypertension: a new target for treatment? *Circulation* **104**, 735–740 (2001).
7. Gibbons, G. H. & Dzau, V. J. The emerging concept of vascular remodeling. *N. Engl. J. Med.* **330**, 1431–1438 (1994).
8. Levy, B. I. *et al.* Effects of chronic inhibition of converting enzyme on mechanical and structural properties of arteries in rat renovascular hypertension. *Circ. Res.* **63**, 227–239 (1988).
9. Levy, B. I., Benessiano, J., Poitevin, P. & Safar, M. E. Endothelium-dependent mechanical properties of the carotid artery in WKY and SHR. Role of angiotensin converting enzyme inhibition. *Circ. Res.* **66**, 321–328 (1990).
10. Schiffrin, E. L. Remodeling of resistance arteries in essential hypertension and effects of antihypertensive treatment. *Am. J. Hypertens.* **17**, 1192–1200 (2004).
11. London, G. M., Asmar, R. G., O'Rourke, M. F. & Safar, M. E. Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: comparison with atenolol. *J. Am. Coll. Cardiol.* **43**, 92–99 (2004).
12. Safar, M. E., Rizzoni, D., Blacher, J., Muiesan, M. L. & Agabiti-Rosei, E. Macro and microvasculature in hypertension: therapeutic aspects. *J. Hum. Hypertens.* **22**, 590–595 (2008).
13. Williams, B. Mechanical influences on vascular smooth muscle cell function. *J. Hypertens.* **16**, 1921–1929 (1998).
14. Agabiti-Rosei, E., Heagerty, A. M. & Rizzoni, D. Effects of antihypertensive treatment on small artery remodelling. *J. Hypertens.* **27**, 1107–1114 (2009).
15. Franklin, S. S. *et al.* Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* **96**, 308–315 (1997).
16. Safar, M. E. *et al.* The Data from an Epidemiologic Study on the Insulin Resistance

Syndrome Study: the change and the rate of change of the age-blood pressure relationship. *J. Hypertens.* **26**, 1903–1911 (2008).
17. Baksi, A. J. *et al.* A meta-analysis of the mechanism of blood pressure change with aging. *J. Am. Coll. Cardiol.* **54**, 2087–2092 (2009).
18. Lieber, A. *et al.* Aortic wave reflection in women and men. *Am. J. Physiol. Heart Circ. Physiol.* doi:10.1152/ajpheart.00985.2009.
19. Darne, B., Girerd, X., Safar, M., Cambien, F. & Guize, L. Pulsatile versus steady component of blood pressure: a cross-sectional analysis and a prospective analysis on cardiovascular mortality. *Hypertension* **13**, 392–400 (1989).
20. Madhavan, S., Ooi, W. L., Cohen, H. & Alderman, M. H. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension* **23**, 395–401 (1994).
21. Blacher, J., Asmar, R., Djane, S., London, G. M. & Safar, M. E. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* **33**, 1111–1117 (1999).
22. Meaume, S., Benetos, A., Henry, O. F., Rudnichi, A. & Safar, M. E. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. *Arterioscler. Thromb. Vasc. Biol.* **21**, 2046–2050 (2001).
23. Avolio, A. P. *et al.* Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension* **54**, 375–383 (2009).
24. Westerhof, N., Stergiopulos, N. & Noble, M. I. M. *Snapshots of Hemodynamics. An Aid for Clinical Research and Graduate Education* (Springer, New York, 2005).
25. London, G. M. *et al.* Arterial wave reflections and survival in end-stage renal failure. *Hypertension* **38**, 434–438 (2001).
26. Westerbacka, J., Seppälä-Lindroos, A. & Yki-Järvinen, H. Resistance to acute insulin induced decreases in large artery stiffness accompanies the insulin resistance syndrome. *J. Clin. Endocrinol. Metab.* **86**, 5262–5268 (2001).
27. Lacolley, P., Safar, M. E., Regnault, V. & Frohlich, E. D. Angiotensin II, mechanotransduction, and pulsatile arterial hemodynamics in hypertension. *Am. J. Physiol. Heart Circ. Physiol.* **297**, H1567–H1575 (2009).
28. Hirai, T., Sasayama, S., Kawasaki, T. & Yagi, S. Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. *Circulation* **80**, 78–86 (1989).
29. Gatzka, C. D., Cameron, J. D., Kingwell, B. A. & Dart, A. M. Relation between coronary artery disease, aortic stiffness, and left ventricular structure in a population sample. *Hypertension* **32**, 575–578 (1998).
30. Stefanadis, C., Wooley, C. F., Bush, C. A., Kolibash, A. J. & Boudoulas, H. Aortic distensibility abnormalities in coronary artery disease. *Am. J. Cardiol.* **59**, 1300–1304 (1987).
31. Jankowski, P. *et al.* Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. *Hypertension* **51**, 848–855 (2008).
32. Agabiti-Rosei, E. *et al.* Central blood pressure measurements and antihypertensive therapy: a consensus document. *Hypertension* **50**, 154–160 (2007).
33. Weber, T. *et al.* Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation* **109**, 184–189 (2004).
34. Safar, M. E. *et al.* Central pulse pressure and mortality in end-stage renal disease. *Hypertension* **39**, 735–738 (2002).
35. Roman, M. J. *et al.* Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension* **50**, 197–203 (2007).
36. Van Bortel, L. M., Struijker-Boudier, H. A. & Safar, M. E. Pulse pressure, arterial stiffness, and drug treatment of hypertension. *Hypertension* **38**, 914–921 (2001).
37. Ingber, D. Integrins as mechanochemical transducers. *Curr. Opin. Cell Biol.* **3**, 841–848 (1991).
38. Wilson, E., Sudhir, K. & Ives, H. E. Mechanical strain of rat vascular smooth muscle cells is sensed by specific extracellular matrix/integrin interactions. *J. Clin. Invest.* **96**, 2364–2372 (1995).
39. Louis, H. *et al.* Role of alpha1beta1-integrin in arterial stiffness and angiotensin-induced arterial wall hypertrophy in mice. *Am. J. Physiol. Heart Circ. Physiol.* **293**, H2597–H2604 (2007).
40. Bézie, Y. *et al.* Fibronectin expression and aortic wall elastic modulus in spontaneously hypertensive rats. *Arterioscler. Thromb. Vasc. Biol.* **18**, 1027–1034 (1998).
41. Kakou, A. *et al.* Selective reduction of central pulse pressure under angiotensin blockage in SHR: role of the fibronectin-alpha5beta1 integrin complex. *Am. J. Hypertens.* **22**, 711–717 (2009).
42. Labat, C. *et al.* Effects of valsartan on mechanical properties of the carotid artery in spontaneously hypertensive rats under high-salt diet. *Hypertension* **38**, 439–443 (2001).
43. Lacolley, P. *et al.* Increased carotid wall elastic modulus and fibronectin in aldosterone-salt-treated rats: effects of eplerenone. *Circulation* **106**, 2848–2853 (2002).
44. Bezie, Y., Lacolley, P., Laurent, S. & Gabella, G. Connection of smooth muscle cells to elastic lamellae in aorta of spontaneously hypertensive rats. *Hypertension* **32**, 166–169 (1998).
45. Koffi, I. *et al.* Prevention of arterial structural alterations with verapamil and trandolapril and consequences for mechanical properties in spontaneously hypertensive rats. *Eur. J. Pharmacol.* **361**, 51–60 (1998).
46. Safar, M. E. *et al.* Peripheral arterial disease and isolated systolic hypertension: the ATTEST study. *J. Hum. Hypertens.* **23**, 182–187 (2009).
47. de Luca, N., Asmar, R. G., London, G. M., O'Rourke, M. F. & Safar, M. E. Selective reduction of cardiac mass and central blood pressure on low-dose combination perindopril/indapamide in hypertensive subjects. *J. Hypertens.* **22**, 1623–1630 (2004).
48. Protogerou, A., Blacher, J., Stergiou, G. S., Achimastos, A. & Safar, M. E. Blood pressure response under chronic antihypertensive drug therapy: the role of aortic stiffness in the REASON (Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind) study. *J. Am. Coll. Cardiol.* **53**, 445–451 (2009).
49. Dhakam, Z. *et al.* A comparison of atenolol and nebivolol in isolated systolic hypertension. *J. Hypertens.* **26**, 351–356 (2008).
50. Guerin, A. P. *et al.* Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* **103**, 987–992 (2001).
51. Kengne, A. P. *et al.* Blood pressure variables and cardiovascular risk: new findings from ADVANCE. *Hypertension* **54**, 399–404 (2009).
52. Williams, B. *et al.* 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 (2006).
53. Matsui, Y. *et al.* Differential effects between a calcium channel blocker and a diuretic when used in combination with angiotensin II receptor blocker on central aortic pressure in hypertensive patients. *Hypertension* **54**, 716–723 (2009).
54. Dengo, A. L. *et al.* Arterial destiffening with weight loss in overweight and obese middle-aged and older adults. *Hypertension* **55**, 855–861 (2010).
55. Ferrario, C. M., Trask, A. J. & Jessup, J. A. Advances in biochemical and functional roles of angiotensin-converting enzyme 2 and angiotensin-(1–7) in regulation of cardiovascular function. *Am. J. Physiol. Heart Circ. Physiol.* **289**, H2281–H2290 (2005).
56. Gueyffier, F. *et al.* Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. INDANA Group. *Lancet* **353**, 793–796 (1999).
57. Asmar, R. G., London, G. M., O'Rourke, M. E. & Safar, M. E. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: a comparison with atenolol. *Hypertension* **38**, 922–926 (2001).

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