Blood pressure regulation during the aging process: the end of the 'hypertension era'?

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The elderly blood pressure paradigm reflects all of the demographic, technological and therapeutic changes over the past 20–30 years that make it now possible to propose a more integrative approach of 'hypertension'. The aim of the present review was to address what does measured blood pressure really mean and what are its determinants during the aging process. We show that standard blood pressure measurements are not adequate or even misleading for the evaluation of cardiovascular risk especially in the elderly patients and that there is a necessity of a transition to a new approach in determining the arterial risk. Direct arterial measurements including analysis of central and peripheral arterial waveforms and assessment of pulse wave velocity can be reliable and easily performed measurements as an alternative to blood pressure-Korotkoff approach. For these measurements, there are currently sufficient clinical data showing their association with cardiovascular risk. There is also the emergence of reference values and beneficial elements of regression by treatment. This new approach as well as recent knowledge on vascular hemodynamics and biology, represent the swan song for the hypertension concept as defined by blood pressure values. *J Hypertens* 29:646–652 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Abbreviations: ABPM, ambulatory blood pressure monitoring; ACCT, Anglo-Cardiff Collaborative Trial; BP, blood pressure; CVD, cardiovascular disease; PP, pulse pressure; PPA, pulse pressure amplification; PWV, pulse wave velocity

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The transition from diastolic to systolic and pulse pressure during aging

Until the ages of 50–60 years, both SBP and DBP increase with age. Thereafter, in the majority of cases, SBP increases with age disproportionally to DBP. The most common cause for the disruption of the correlation between SBP and DBP (leading to an excessive increase in SBP and pulse pressure (PP)) is the progressive stiffening of the arterial wall [1,2].

The reasons of the increase in pulse pressure with age

Wall hypertrophy, calcium deposits, increase in collagen and in fibronectin, fragmentation and disorganization of the elastin network, nonenzymatic crosslinks and cell–matrix interactions, are the predominant structural determinants of the decrease in elastic properties and the development of large artery stiffness and increase in PP [3].

It is important at this juncture to point out that SBP is dependent on left ventricular performance and on the stiffness of the aorta and other large arteries [1]. Thus, peak systolic pressure will be greater if the arterial wall is more rigid. Minimum diastolic pressure is determined by the duration of the diastolic interval and the rate at which pressure falls. The rate of fall in pressure is influenced by the rate of outflow, that is peripheral resistance, and by viscoelastic arterial properties. At a given vascular resistance, the drop in diastolic pressure will be greater if the rigidity of large arteries is increased.

Several clinical cross-sectional and longitudinal studies have shown that increase in arterial stiffness with age is not linear, being more pronounced after the age of 55–60 [4], which may in turn explain the more pronounced increase in PP after this age reported in the Framingham study [5]. In addition to age, any disease and/or situation that induces an accelerated increase in arterial stiffness will be clinically expressed by an increase in SBP and PP. Diabetes is a typical example of accelerated arterial aging leading to a more noticeable increase in PP with age as compared to nondiabetic patients, due to a more pronounced increase in arterial stiffness [6].

The increasing impact of systolic/pulse pressure in the elderly

Taking into account these considerations can better explain why SBP and PP better reflect cardiovascular disease (CVD) risk in older patients, whereas DBP better reflects the risk in younger patients [7]. Indeed, DBP in young patients is predominantly dependent on peripheral resistance and therefore low DBP reflects low peripheral resistance. In addition, in younger patients with hyperkinetic circulation, DBP is less variable than SBP, thus better reflecting cardiovascular risk. In older patients, a low DBP may reflect high arterial stiffness which is a major manifestation of arterial aging, rather than low peripheral resistance [1,2]. In this case, low DBP is associated with high SBP and high PP and increased

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cardiovascular risk. The clinical application of these considerations is that, as clearly stated in the latest guidelines of the JNC, 'in persons older than 50 years, SBP is a much more important cardiovascular risk factor than DBP' [8].

Also, in 2003, for the first time the ESH–ESC guidelines on the management of hypertension [9] have suggested that PP may represent an independent risk factor, and that therapeutic studies should henceforth be conducted to assess the benefits of reducing PP in terms of cardiovascular morbidity and mortality, especially among those over 60 years of age [7]. Indeed, since the first study, conducted in 1989, which demonstrated a positive association between PP and target organ damage [10], a large number of clinical studies notably over the past 10 years have shown that increased PP is a strong predictor of coronary disease, incidence of heart failure, and cardiovascular morbidity and mortality, independently of mean blood pressure (BP) levels [5,11]. Such observations have been made in a variety of different populations but are apparently more pronounced in diabetics and elderly patients. Threshold PP risk values have been proposed, notably a value of approximately 65 mmHg [12,13].

The SBP/pulse pressure-related increase in cardiovascular risk: is it only a barometric phenomenon?

To date at least three hypotheses can be put forward to explain the association between SBP/PP and cardiovascular risk. Actually, these three hypotheses are complementary rather than contradictory:

(1) PP and increased cyclic stress. Experimental studies indicate that fatigue and fracture of elastic fibers within the arterial wall are related to both steady-state and pulsatile stress [14]. *In vivo*, the former is primarily dependent on mean arterial pressure, whereas the latter is related to amplitude of PP and also to heart rate. Therefore, increased PP by itself could be responsible for cardiac and arterial fatigue and subsequent complications such as left ventricular hypertrophy, arterial hypertrophy and dilatation, endothelial damage and extracellular matrix changes.
(2) Altered ventricular–aortic coupling influences myocardial perfusion by elevating the proportion of coronary flow during the systolic time period [15]. Thus, increased PP and low DBP lead to decreased coronary perfusion.
(3) PP is associated with CVD risk because it is an indicator of arterial stiffness; therefore PP is merely an epiphenomenon and not responsible for cardiovascular alterations. We believe that this third hypothesis is the main explanation of the relationship SBP/PP and CVD morbid-mortality. This assumption is based on the fact that the risk related to PP is mainly observed in the elderly and is due to both high SBP and low DBP [5,7] reflecting the typical clinical manifestations of arterial aging.

In a community-based study among patients 85 years of age or older, survival was lower in patients with low SBP and DBP [16]. This paradox appears to be related to the presence of co-morbidities since it was no longer present after adjusting for confounding parameters. However, after these statistical adjustments, no positive relationship was found between BP and cardiovascular morbidity and mortality indicating that BP may not be a risk indicator in this group of patients. Other studies in elderly patients have shown that a decrease in BP over a long period of time predicts high morbidity and mortality [17]. In a recent study in the United States conducted in institutionalized patients, no relationship was observed between BP levels and cardiovascular risk [18]. Hence, the absence of association between BP and CVD risk in the very elderly appears to be linked to several age-related changes as summarized below:

(1) The presence of frequent co-morbidities in the very elderly, in particular denutrition, heart failure and several neurological disorders, reduces BP levels, thereby masking the association between high BP and CVD risk [19].
(2) Exaggeration of BP variability, mainly SBP and PP variability, due to alterations in homeostatic mechanisms. Arterial stiffness, baroreceptor failure and neurological diseases are responsible for this variability and for the presence of orthostatic or postprandial hypotension [20]. Therefore, SBP and PP recorded during casual measurements may not reflect more permanent SBP and PP levels.
(3) Finally, we should mention the relatively frequent overestimation of BP levels in the presence of severe mediacalcosis (pseudo-hypertension) [21] due to the lack of compressibility of peripheral arteries.

These data point out that standard BP measurements are not adequate or even misleading for the evaluation of CVD risk in the very elderly frail patients. All the same, remains still irreplaceable the role of the standard blood pressure measurements in particular clinical settings, for example in patients with sepsis and other unstable hemodynamic situation.

Influence of arterial aging on the response to antihypertensive treatment

Beyond this epidemiological evidence, the response to antihypertensive treatments clearly shows that arterial aging should be taken into account in order to answer a number of questions: Why is SBP not controlled in the majority of treated hypertensives? Is there an optimal BP decrease? What is the J-shape curve threshold for DBP, SBP and PP? Should we be apprehensive of an excessive decrease of BP in frail patients?

Failure to control SBP

The recent reappraisal of European guidelines on hypertension management [22] suggested that SBP should be under 140 mmHg and that DBP be under 90 mmHg for all treated hypertensive patients, independently of the presence of associated risk factors and or CVD. Observational studies from several countries have demonstrated that among treated hypertensive individuals, the proportion of those who are well controlled is less than 30% [23]. In a study conducted in a general elderly population (over 60 years of age) in Nancy (northeast part of France), we found that only 50% of treated patients were well controlled, that is SBP less than 140 mmHg and DBP less than 90 mmHg [24]. Among uncontrolled patients, 84% were uncontrolled only for SBP (>140 mmHg), 14% for both SBP and DBP (>90 mmHg) while only less than 2% were controlled for SBP but uncontrolled for DBP. These results are of importance in the prognosis of treated patients, since lack of control of SBP (but not DBP) has been shown to be a major determinant of mortality in treated hypertensives [25].

Several factors can contribute to a poor control of high SBP. Among these, the increasing prevalence of obesity, sedentary life and high-salt diet can contribute to the resistance of antihypertensive treatment [26]. In our opinion, arterial aging-stiffening is the main determinant which could explain current failure in controlling systolic but not DBP. Aging of the population, in association with increasing prevalence of obesity and metabolic problems, results in the fact that an increasing number of people present substantial arterial stiffness, hence leading to increased SBP and PP. In other words, hypertensive patients treated in 2010 are very different in comparison to hypertensives we used to treat back in the 1980s. Hence, even despite the use of combination therapies, SBP in most patients remains well above the goals determined by international guidelines.

Blood pressure drop with treatment: the 'J-shape curve': which are the thresholds for 'clinical relevant', 'optimal' and 'harmful' levels

Classically, a clinical relevant decrease in BP following antihypertensive treatment signifies a decrease by at least 6–7 mmHg, since this threshold is considered to be associated with a significant decrease in cardiovascular complications [8]. We believe that in order to correctly answer this question we must follow a different approach: the clinical relevant decrease in BP is the one that results from an improvement in arterial function. In other words, a permanent progressive decrease in DBP and SBP of 10 mmHg in a 50-year-old hypertensive patients with a pre-treatment level of 160/100 mmHg, can be considered as clinically relevant as it is certainly due to a significant improvement in microcirculation and a decrease in peripheral vascular resistance. On the contrary, the same decrease in DBP but without a decrease in SBP in a 72-year-old diabetic patient with an initial BP of 175/100 is clearly a bad sign since it reflects the incapacity of the drug to reduce arterial stiffness which is the main determinant of systolic hypertension in this patient.

The 'J-curve' describes the relationship between BP and the risk of cardiovascular morbidity and/or mortality. Cardiovascular risk is high for an elevated BP level, and is reduced in parallel with BP reduction until a nadir is reached, below which further BP reduction increases risk [27,28]. Several studies have shown that a 'J-curve' exists mainly between DBP and coronary disease especially in the frailest patients [27].

Thus, the 'J-curve' legitimately brings the motto 'the lower the better' into question, and confirms the need for using further diagnostic methods to evaluate arterial hypertension and personalizing the treatment. In a situation of hypertension characterized by preserved viscoelastic properties of large arteries, an antihypertensive treatment may determine a reduction in SBP without significant change in DBP, due to the delay and redistribution of reflected waves in the diastolic phase. In this condition, lowering BP can improve coronary perfusion. By opposition, in the presence of large artery stiffening, antihypertensive treatment can excessively reduce DBP levels and notably proto-diastolic pressure, hence contributing to a reduction in coronary flow. Thus, the association between the lowering of BP and the increase in cardiovascular risk recorded in clinical trials most likely results from marked arteriosclerosis and/or a previous unknown coronary artery disease [28].

Alternative to the casual blood pressure measurements for a more accurate evaluation of the 'hemodynamic' risk

There is currently ample data to conclude that other than standard BP measurements are needed in order to better assess the so-called BP-related risk, especially in the elderly.

(1) Multiple more ecological measurements including self-measurements and 24-h ambulatory blood pressure monitoring (ABPM).
(2) Pulse wave analysis and evaluation of wave reflections.
(3) Central pulse pressure and central to peripheral pressure amplification.
(4) Direct arterial stiffness assessment by measuring pulse wave velocity.

Increasing the number of measurements (self-measurements and 24-h ambulatory blood pressure monitoring)

Several studies have shown that in the elderly, ambulatory (24-h ABPM) [29] or self-measured [30] BP is a better predictor of cardiovascular risk than clinical BP.

These data indicate that elderly patients with increased clinical but normal self-measured BP or low 24-h ABPM were at much lower risk than those with equivalent clinical BP levels but also high self measured and 24-h ABPM. For these reasons, several recent guidelines for the management of high BP suggest systematically performing self-measurements in community-living elderly [31].

However, this approach can only resolve part of the problem since it cannot assess the problems related to arterial aging and the discrepancies between BP levels and cardiovascular risk.

Focus on pulse wave analysis

Frederick Akbar Mahomed, a half-Indian half-British physiologist who lived in Great Britain during the nineteenth century, developed the concept and techniques of pulse waveform analysis. Unfortunately, this approach has been largely ignored for at least two reasons: firstly because Frederick Akbar Mahomed died in 1884 at the very early age of 32 years and secondly because a few years later, Riva Rocci and Korotkoff introduced the cuff sphygmomanometer, a device much easier to use, although unequivocally yielding less information with regard to arterial function. Over recent years, pulse waveform analyses have experienced somewhat of a revival. Using accurate tonometric recordings at different arterial sites (radial, carotid), analysis of pressure waves by various algorithms [32] is able to estimate ascending aortic waveform. These waveforms are not only able to provide quantitative information regarding central BP levels but also qualitative data relative to the waveforms themselves, thereby enabling definition of the elastic properties of the arterial wall [14,32]. These validated noninvasive techniques, are able to quantify the amplification of pressure by reflected waves and represent a reliable marker of overall arterial health.

Pressure wave reflections and blood pressure amplification

BP amplification is defined by the elevation of PP from the central aorta toward the periphery and is mainly attributed to the elevation of SBP [14,32]. Pressure wave amplification can be explained by the reflection phenomena of the pulsatile BP wave. Propagation of the BP wave is achieved from the heart to the periphery at a celerity corresponding to the pulse wave velocity (PWV). Depending on the PWV and the distance covered, the reflected wave generated at the periphery will add to the forward BP wave, at a more or less earlier time frame during the cardiac cycle. In the presence of a low stiffness-low PWV state, the reflected waves will therefore arrive during the systolic phase only in peripheral arteries (i.e. radial arteries) which are in very close proximity to the reflection sites. In this state, the arrival of the reflected waves at the central arteries will occur later during the diastolic period and therefore will not contribute to increasing systolic and pulse pressure. This mechanism explains the amplification of the PP wave, that is why peripheral (brachial) pulse pressure is higher than central (aortic or carotid) pulse pressure.

The PP amplification (PPA) may be expressed as a percentage increase: PPA (%) = 100 * (peripheral PP − central PP)/central PP. The Anglo-Cardiff Collaborative Trial (ACCT) [32] has shown that the ratio of brachial/central PP varies from 70% at less than 20 years of age to 20% at over 80 years of age. When expressed as the absolute change in mmHg, the difference between brachial and central PP varies from 20 to 7 mmHg.

The disappearance of aortic-brachial PPA, together with an increase in central PP and in PWV, were shown to be significant predictors of all-cause and cardiovascular mortality [14,33–39], and in the very elderly, low PPA is associated with higher prevalence of heart disease [40]. In addition, the predictive power of PPA was superior to peripheral and carotid PP [33]. An increase of 1 SD in PPA was associated with a 19% increase of all-cause mortality and a 30% increase in cardiovascular mortality [14,34,35].

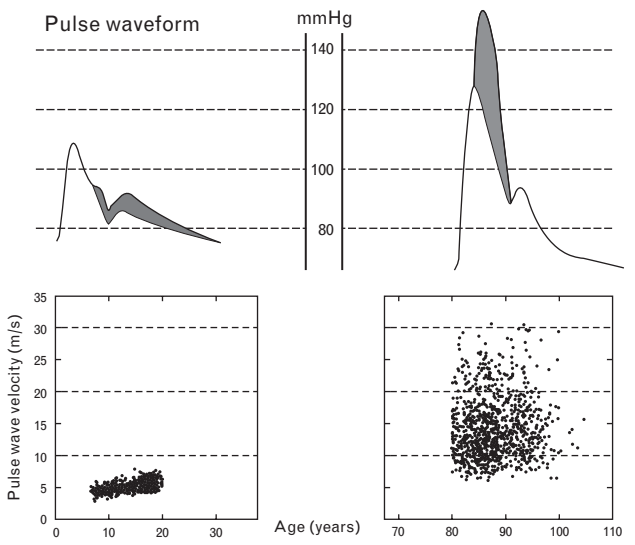
Arterial stiffness measured by pulse wave velocity

PWV is the speed with which the pulse wave spreads across an arterial segment [14]. Aortic (carotid-femoral) PWV is an established method for characterizing aortic stiffness [41]. Increase in PWV with age is not linear [42], being more pronounced after the age of 55–60 (Fig. 1) [4,43]. Hence, the annual increase in PWV before the age of 50 is approximately 100 mm/s (i.e. an annual increase of about 1%) and rises to an annual increase of more than 150 mm/s after the age of 60. This age-related increase pertains essentially to aortic PWV, conventionally measured between the carotid and femoral arteries, and much less to PWV measured in peripheral arteries, particularly of the upper and lower limbs [4].

The relationship between aortic PWV and cardiovascular morbidity and mortality has been demonstrated not only in the general population but also in subgroups of patients, especially among hypertensive and diabetic patients, coronary patients, very old patients and hemodialysis patients [44–46]. Risk assessment by use of the Framingham equations has indeed allowed demonstration that this cardiovascular risk was linearly correlated with the sole measurement of PWV [47].

In a clinical trial, Guerin *et al.* [48] have shown that survival of end-stage renal failure patients was strongly related to the drug-induced reversibility of aortic stiffness measured by PWV independently of BP evolution. This result highlights that, especially in patients with a pronounced arterial aging, PWV predicts better than BP benefits of antihypertensive treatment.

Fig. 1



Upper panel: pulse waveform in young (left) and in elderly (right). In the elderly, aortic stiffness leads to an increase in systolic peak in forward wave and a reduction in DBP. Moreover, arterial stiffness determines an earlier forward and backward wave interaction, leading to a further increase in systolic peak. In young patients the overlapping between forward and backward waves occurs during telo-systolic and diastolic phases. The contribution of reflected waves is highlighted in gray color. Lower panel: pulse wave velocity values determined by a high-fidelity arterial tonometer in 1001 young patients under 20 years [51] (mean $\pm$ SD: 5.2 ± 0.8 m/s) and in 1042 patients over 80 years [4] (mean $\pm$ SD: 14.2 ± 4.8 m/s). This almost three-fold increase of pulse wave velocity in the elderly is the main cause of the early arrival of reflected waves during the systolic period as indicated in the upper panel.

The 2007 ESH–ESC guidelines on the management of hypertension [49] recognized for the first time the independent role of PWV in the risk of cardiovascular morbidity and mortality. These guidelines have hence proposed that a PWV higher than 12 m/s should be regarded as an abnormally high value and thus associated with increased cardiovascular risk. Recent studies attempt now to establish reference values in various populations [50–52].

Future directions: the end of the arterial hypertension concept?

Changes in the dogma of the relationship between BP and cardiovascular risk is the first example of the fact that the most important thing is not how high or low is your BP, but the reason why your BP is low or high.

Hence, the important issue in epidemiology is the personal history of each patient. The question is therefore which parameter can best describe a person's 'personal history'. BP in younger and middle-age people without excessive arterial aging can describe the arterial history in a relatively fair and appropriate manner. In these patients, complementary explorations could add some important information on target organ damage, although the simplicity of BP measurements has made this measurement a gold standard. However, as patients get older, or exhibit accelerated aging as a consequence of obesity, diabetes, renal insufficiency, etc., BP becomes a 'poor story teller' and may be misleading in the understanding of the underlying arterial state. The elderly BP paradigm is the clearest example for the necessity of a transition from the BP-Korotkoff model to a new approach in determining the arterial profile. This new approach as well as recent knowledge on vascular hemodynamics and biology, represent the swan song for the hypertension concept as defined by BP measurement values.

Although there are many strong arguments to promote direct arterial measurements such as pulse wave analysis and PWV instead of standard BP, there is still a lack of interventional studies to show the superiority of pulse wave analysis and PWV in the improvement of cardiovascular events.

We propose a realistic two-step strategy based on the timing of the application of this new approach in the evaluation of arterial status:

(1) On the short term, direct arterial measurements including analysis of central and peripheral arterial waveforms and assessment of PWV can be reliable and easily performed measurements as an alternative to BP-Korotkoff. For these measurements, there are currently sufficient clinical data showing their association with cardiovascular risk. There is also the emergence of reference values and beneficial elements of regression by treatment. Presently, therapeutic trials should be focused on these arterial parameters rather than on the simple BP-Korotkoff model.
(2) On the long term, these measurements should be complemented by new biomarkers of arterial ageing, vessel wall inflammation, fibrosis and genetics, as well as new molecular imaging techniques.

One could argue that this two-step approach may be considered as arbitrary or limitative and that much more testing is needed to define an exhaustive arterial profile. We believe, however, that this is the unique realistic way in order to change the current clinical practice which is, and will be in the near future, insufficient for managing patients with 'very aged arteries'.

In a more general facet, BP values should be integrated within the individual's overall cardiovascular homeostasis but also to his/her general health status. Achieving the right prevention is not solely to treat 'numbers' that show 'strong correlation with risk', but rather attempting to clarify what lies beneath these 'numbers'. It is therefore important to consider BP values as signs of a physiological balance and homeostasis (or an imbalance thereof) rather

than to focus our attention on so-called 'magical' numbers.

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References

1 Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation* 2003; **107**:2864–2869.
2 O'Rourke M, Frohlich ED. Pulse pressure: is this a clinically useful risk factor? *Hypertension* 1999; **34**:372–374.
3 Lakatta EG. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises. Part III: Cellular and molecular clues to heart and arterial aging. *Circulation* 2003; **107**:490–497.
4 Benetos A, Buatois S, Salvi P, Marino F, Toulza O, Dubail D, *et al.* Blood pressure and pulse wave velocity values in the institutionalized elderly aged 80 and over: baseline of the PARTAGE study. *J Hypertens* 2010; **28**:41–50.
5 Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation* 1999; **100**:354–360.
6 Ronnback M, Fagerudd J, Forsblom C, Pettersson-Fernholm K, Reunanen A, Groop PH. Altered age-related blood pressure pattern in type 1 diabetes. *Circulation* 2004; **110**:1076–1082.
7 Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, *et al.* Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation* 2001; **103**:1245–1249.
8 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, *et al.* Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003; **42**:1206–1252.
9 European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**:1011–1053.
10 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* 1989; **13**:392–400.
11 Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetieere P, *et al.* Pulse pressure: a predictor of long-term cardiovascular mortality in a french male population. *Hypertension* 1997; **30**:1410–1415.
12 De Simone G, Roman MJ, Alderman MH, Galderisi M, de Divitiis O, Devereux RB. Is high pulse pressure a marker of preclinical cardiovascular disease? *Hypertension* 2005; **45**:575–579.
13 Gasowski J, Fagard RH, Staessen JA, Grodzicki T, Pocock S, Boutitie F, *et al.* Pulsatile blood pressure component as predictor of mortality in hypertension: a meta-analysis of clinical trial control groups. *J Hypertens* 2002; **20**:145–151.
14 Nichols WW, O'Rourke M. *Blood flow in arteries. Theoretical, experimental and clinical principles*, 5th ed. London, UK: Edward Arnold; 2005.
15 Kass DA. Ventricular arterial stiffening: integrating the pathophysiology. *Hypertension* 2005; **46**:185–193.
16 Boshuizen HC, Izaks GJ, van Buuren S, Ligthart GJ. Blood pressure and mortality in elderly people aged 85 and older: community based study. *BMJ* 1998; **316**:1780–1784.
17 Satish S, Zhang DD, Goodwin JS. Clinical significance of falling blood pressure among older adults. *J Clin Epidemiol* 2001; **54**:961–967.
18 Askari M, Kiely DK, Lipsitz LA. Is pulse pressure a predictor of cardiovascular complications in a frail elderly nursing home population? *Aging Clin Exp Res* 2004; **16**:206–211.
19 Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, *et al.* 15-Year longitudinal study of blood pressure and dementia. *Lancet* 1996; **347**:1141–1145.
20 Vanhanen H, Thijs L, Birkenhager W, Bulpitt C, Tilvis R, Sarti C, *et al.* Prevalence and persistency of orthostatic blood pressure fall in older patients with isolated systolic hypertension. Syst-eur investigators. *J Hum Hypertens* 1996; **10**:607–612.
21 Mac Mahon M, Sheahan NF, Colgan MP, Walsh B, Malone J, Coakley D. Arterial closing pressure correlates with diastolic pseudohypertension in the elderly. *J Gerontol A Biol Sci Med Sci* 1995; **50A**:M56–M58.
22 Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, *et al.* Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 2009; **27**:2121–2158.
23 Burt VL, Cutler JA, Higgins M, Horan MJ, Labarthe D, Whelton P, *et al.* Trends in the prevalence, awareness, treatment, and control of hypertension in the adult us population. Data from the health examination surveys, 1960 to 1991. *Hypertension* 1995; **26**:60–69.
24 Perret-Guillaume C, Miget P, Aubry C, Gueguen R, Steyer E, Benetos A. Blood pressure control by antihypertensive agents in people older than 60. *Rev Med Interne* 2006; **27**:285–290.
25 Benetos A, Thomas F, Bean K, Gautier S, Smulyan H, Guize L. Prognostic value of systolic and diastolic blood pressure in treated hypertensive men. *Arch Intern Med* 2002; **162**:577–581.
26 Chobanian AV, Shattuck lecture. The hypertension paradox: more uncontrolled disease despite improved therapy. *N Engl J Med* 2009; **361**:878–887.
27 Kannel WB, Wilson PW, Nam BH, D'Agostino RB, Li J. A likely explanation for the J-curve of blood pressure cardiovascular risk. *Am J Cardiol* 2004; **94**:380–384.
28 Messerli FH, Panjrath GS. The J-curve between blood pressure and coronary artery disease or essential hypertension: exactly how essential? *J Am Coll Cardiol* 2009; **54**:1827–1834.
29 Staessen JA, Thijs L, O'Brien ET, Bulpitt CJ, de Leeuw PW, Fagard RH, *et al.* Ambulatory pulse pressure as predictor of outcome in older patients with systolic hypertension. *Am J Hypertens* 2002; **15**:835–843.
30 Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, *et al.* Cardiovascular prognosis of 'Masked hypertension' detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 2004; **291**:1342–1349.
31 Management of adults with essential hypertension: 2005 update – guidelines. *J Mal Vasc* 2006; **31**:16–33.
32 McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: The Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* 2005; **46**:1753–1760.
33 Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM, *et al.* Central pulse pressure and mortality in end-stage renal disease. *Hypertension* 2002; **39**:735–738.
34 Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, *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* 2006; **113**:1213–1225.
35 Benetos A, Thomas F, Joly L, Blacher J, Pannier B, Labat C, *et al.* Pulse pressure amplification a mechanical biomarker of cardiovascular risk. *J Am Coll Cardiol* 2010; **55**:1032–1037.
36 Avolio A. Central aortic blood pressure and cardiovascular risk: a paradigm shift? *Hypertension* 2008; **51**:1470–1471.
37 Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, *et al.* Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension* 2009; **54**:375–383.
38 Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Lamm G, *et al.* Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. *Eur Heart J* 2005; **26**:2657–2663.
39 Chirinos JA, Zambrano JP, Chakko S, Veerani A, Schob A, Willens HJ, *et al.* Aortic pressure augmentation predicts adverse cardiovascular events in patients with established coronary artery disease. *Hypertension* 2005; **45**:980–985.
40 Salvi P, Safar ME, Labat C, Borghi C, Lacolley P, Benetos A. Heart disease and changes in pulse wave velocity and pulse pressure amplification in the elderly over 80 years: The PARTAGE study. *J Hypertens* 2010; **28**:2127–2133.
41 Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, *et al.* Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; **27**:2588–2605.
42 Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, *et al.* Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: The Framingham Heart Study. *Hypertension* 2004; **43**:1239–1245.

43 Benetos A, Adamopoulos C, Bureau JM, Temmar M, Labat C, Bean K, *et al.* Determinants of accelerated progression of arterial stiffness in normotensive subjects and in treated hypertensive subjects over a 6-year period. *Circulation* 2002; **105**:1202–1207.
44 Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, *et al.* Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; **37**:1236–1241.
45 Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002; **106**:2085–2090.
46 Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, *et al.* Arterial stiffness and risk of coronary heart disease and stroke: The Rotterdam Study. *Circulation* 2006; **113**:657–663.
47 Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension* 1999; **33**:1111–1117.
48 Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001; **103**:987–992.
49 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, *et al.* 2007 guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**:1105–1187.
50 Alecu C, Labat C, Kearney-Schwartz A, Fay R, Salvi P, Joly L, *et al.* Reference values of aortic pulse wave velocity in the elderly. *J Hypertens* 2008; **26**:2207–2212.
51 Reusz GS, Cseprekal O, Temmar M, Kis E, Cherif AB, Thaleb A, *et al.* Reference values of pulse wave velocity in healthy children and teenagers. *Hypertension* 2010; **56**:217–224.
52 The Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010; **31**:2338–2350.