Curr Atheroscler Rep (2014) 16:387
DOI 10.1007/s11883-013-0387-8

CORONARY HEART DISEASE (JA FARMER, SECTION EDITOR)

Arterial Stiffness as a Risk Factor for Coronary Artery Disease

Josh Liao · John Farmer

Published online: 9 January 2014

Abstract Hypertension is a major modifiable risk factor, and clinical trials have demonstrated that successful reduction of elevated blood pressure to target levels translates into decreased risk for the development of coronary artery disease, stroke, heart failure, and renal failure. The arterial system had previously been regarded as a passive conduit for the transportation of arterial blood to peripheral tissues. The physiologic role the arterial system was greatly expanded by the recognition of the central role of the endothelial function in a variety of physiologic processes. The role of arterial function and structure in cardiovascular physiology was expanded with the development of a variety of parameters that evaluate arterial stiffness. Markers of arterial stiffness have been correlated with cardiovascular outcomes, and have been classified as an emerging risk factor that provides prognostic information beyond standard stratification strategies involving hypertension, diabetes, obesity, dyslipidemia and smoking. Multiple epidemiologic studies have correlated markers of arterial stiffness such as pulse-wave velocity, augmentation index and pulse pressure with risk for the development of fatal and nonfatal cardiovascular events. Additionally, measurements of arterial stiffness had clarified the results of clinical trials that demonstrated differing impacts on clinical outcomes, despite similar reductions in blood pressure, as measured by brachial and sphygmomanometry.

This article is part of the Topical Collection on *Coronary Heart Disease*

J. Liao
Department of Medicine, Peter Bent Brigham Hospital, Harvard Medical School, Boston, MA, USA

J. Farmer (✉)
Department of Medicine, Baylor College of Medicine, Houston, TX, USA
e-mail: jfarmer@bcm.tmc.edu

Keywords Arterial stiffness · Pulse-wave velocity · Cardiovascular risk · Pulse pressure · Augmentation index · Hypertension · Wave reflection

Introduction

Over the past several decades, age-adjusted cardiovascular mortality has been steadily decreasing in the United States. The precise mechanism that underlies this encouraging decline in vascular events is multifactorial, and relates to improvements in both diagnostic and therapeutic interventions. However, cardiovascular disease remains the leading cause of death in the United States and the developed world. Despite the improved capacity to identify individuals at risk for the development of vascular disease, the lack of a unifying hypothesis that explains all aspects of the initiation and progression of atherosclerosis has limited definitive therapy. The process of atherosclerosis is best regarded as a syndrome with multiple factors influencing the pathophysiologic processes that are involved in the initiation and progression of vascular disease. The concept of risk factor identification and modification has gained credence as a means to stratify individuals at risk for the development of vascular disease and initiate therapy. Clinical trials have demonstrated that identification and modification of the classic cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes mellitus, and tobacco consumption, by lifestyle interventions or pharmacologic treatment will decrease the risk for the development of subsequent cardiovascular events. However, improvement in the identification and risk stratification strategies is clearly needed due to the high residual prevalence of cardiovascular events despite institution of therapeutic interventions. Additionally, individuals who would appear to exhibit a relatively modest risk factor profile have been demonstrated to suffer a

cardiovascular event, which emphasizes the need for more precise stratification.

Historically, the arterial system had been regarded as a passive conduit that allowed transport of oxygenated blood and nutrients to the peripheral tissues. However, the recognition of the active role of the endothelium in a multiplicity of previously unappreciated physiologic activities, including vascular tone, lipoprotein transport, coagulation, platelet activity and inflammation, has generated increased interest in the physiologic activity of the arterial tree beyond the conduit function. The initiation of physiologic abnormalities in endothelial function has been recognized as the first identifiable phase in the development of atherosclerosis. Additionally, identification of genetic influences and signaling pathways involved in the initiation of atherosclerosis have been refined, and provided insight into the early phases of the development of vascular disease [1••]. Increased clinical and experimental evidence has implicated progressive modification of the structure and function of the vascular system mediated by a variety of cardiovascular risk factors, especially hypertension, in the initial phases of atherosclerosis. Hypertension is a major modifiable cardiovascular risk factor, and vascular changes associated with the aging process are especially prominent with progressive elevation of systolic and diastolic pressure, which predate clinically identifiable atherosclerosis [2]. Progressive alteration of arterial structure and function may be both a consequence of elevated blood pressure, and additionally may play a pathogenetic role in the development of and persistence of hypertension. Exposure of the arterial bed to elevated levels of systolic and diastolic blood pressure is associated with a remodeling process that involves a variety of pathologic processes, including hypertrophy and hyperplasia of smooth muscle cells within the vascular tree, coupled with the modification of matrix proteins which play a pivotal role in the initiation and progression of atherosclerosis [3]. The continuous deposition of a variety of proteins, including collagen, coupled with progressive loss of the elastic matrix will result in arterial stiffening. Additionally, progressive deposition of calcium further results in increased arterial stiffness, which is amplified in hypertensive patients with end organ damage such as renal insufficiency [4•]. The progressive remodeling process that occurs with the aging process results in a loss of vascular compliance, which is characterized by a diminished ability of vascular relaxation following systolic ejection of the cardiac output into the central circulation. The reduction in the ability of the arterial tree to dilate due to maladaptive structural changes in the vascular system may be considered to be a significant factor in the initiation and progression of hypertension. Persistent arterial stiffening initiates a vicious cycle with a structural modification of the resistance and capacitance vessels that may subsequently become fixed, resulting in a progressive reduction of vascular compliance. Arterial stiffness may be assessed by a variety of methods, and has been linked to increased risk for the development of atherosclerosis, as well as been utilized as a prognostic marker beyond standard risk factor stratification [5]. Reproducible measurements and quantification of aortic stiffness by methods such as the determination of pulse wave velocity and augmentation index have been demonstrated to be predictive of subsequent coronary events. The quantification of arterial stiffness may improve cardiovascular risk stratification and therapy in high-risk individuals [6]. Additionally, modification of arterial stiffness provides a potential therapeutic target for intervention to potentially reduce cardiovascular events. This review will focus on methods to quantitate arterial stiffness and factors that alter the initiation and progression of vascular changes, which may provide prognostic insight for the role of arterial stiffness as an emerging risk factor for the development of coronary artery disease with special emphasis on the development of hypertension.

Physiologic Determinants of Arterial Compliance

The arterial bed receives the cardiac output, which is delivered in a pulsatile fashion with intermittent flow following cardiac systole. The arterial system demonstrates a degree of compliance that results in a cushioning effect and converts the cardiac output to relatively steady flow within the peripheral vessels. The arterial system can be divided into two major functional categories. The large elastic arteries demonstrate a significant degree of compliance, and can accommodate large volumes of blood during systole while minimizing changes in pressure due to the highly developed and distensible media, which is composed of concentric layers of elastic fibers [7]. Additionally, the distally located intermediate-size muscular arteries exhibit a thick media, which is composed of vascular smooth muscle fibers and regulates the distribution of regional blood flow by variations in vascular tone. The compliance of the arterial tree is modified as the vessels undergo progressive branching into smaller muscular vessels that are characterized by a significantly higher resistance. The pressure wave generated during systole is propagated into the periphery, and additionally a second pressure wave is generated from the resistance vessels by reflection in a retrograde fashion into the central circulation. The reflected waves contribute to the characteristic pressure wave morphology in the aorta, which can be quantitated. The magnitude of the reflected waves is highest at the site of origin, which provides a physiologic rationale as a means to explain the increased systolic pressure within the peripheral vessels relative to the central circulation [8, 9]. The expansile properties of the muscular and elastic arteries are limited to a degree, which results in an increase in the systolic pressure. The aorta is characterized by a significant degree of elastic recoil that acts as a physiologic

mechanism to maintain forward flow during diastole. During the aging process, the arterial system loses compliance and progressive stiffening occurs. The aging process alters the arterial media, which is a combination of vascular smooth muscle cells and variable degrees of elastic tissue. Additionally, progressive modification of the intima, which is populated by endothelial cells and the elastic lamina, occurs with age. The degree of aortic stiffening with age is multifactorial and is mediated by a variety of structural and functional alterations that progressively occur over time. The arteries are exposed to shearing forces and a variety of local atherogenic factors that result in alteration of vascular structure and function characterized by increases in luminal diameter, aortic stiffness and the impact of reflected waves from the periphery [10]. During the aging process, the elastin the aorta is progressively replaced by deposition of collagen. Additionally, intimal thickening occurs, which leads to progressive arterial dilation and rigidity, and is accompanied by smooth muscle cells migration from the media [11]. Wall stress is determined by the pressure within the vessel and the radius according to the Law of Laplace (wall stress= pressure x radius/2 x wall thickness). The thickening of the vessel wall is mediated by vascular cell hypertrophy, and hyperplasia results in maintenance of the tensile strength of the vessel. Vascular remodeling is characterized by a reduction amount of elastic elements and results in a progressive diminution of compliance. The elastic components of the large arteries allow intermittent expansion with subsequent contraction due to vascular recoil. The physiologic distensibility of the vessel is adversely affected by a progressive reduction in the degree of elastic tissue coupled with enhanced collagen deposition and vascular calcification. Additionally, smooth muscle cells undergo functional changes due to hypertrophy and surrounding fibrosis, which also alter the elastic properties of the artery. The progressive noncompliant artery will demonstrate an increase in systolic pressure and a fall in diastolic pressure that progressively occurs with the aging process. Clinical studies have determined that the systolic blood pressure progressively increases with age. Observational data obtained from the Framingham Heart Study demonstrated a linear increase in systolic blood pressure from age 30 through age 84 [12]. Additionally, mean arterial pressure and diastolic pressure also initially increased with age. However, diastolic blood pressure tends to fall after age 50, resulting in a significant rise in pulse pressure (systolic blood pressure minus diastolic blood pressure). The hemodynamic changes that occur with the aging process are felt to be secondary to increased large artery stiffness, rather than burned out diastolic hypertension or selective survivorship. The progressive increase in systolic blood pressure results in an increase in arterial stiffness, with perpetuation by a vicious cycle. The elastic properties of the vascular tree can be determined by a variety of physiologic parameters that evaluate the arterial stiffness [13•].

Pulse Pressure

The physiologic parameter that is most easily quantitated is the measurement of the pulse pressure, which is simply the difference between the systolic and diastolic pressures obtained at the brachial artery utilizing a sphygmomanometer. The pulse pressure can be considered to be reflective of the pulsatile nature of the transmitted cardiac output. Pulse pressure has been utilized as a determinant of cardiovascular risk, and increased pulse pressure has been associated with an increased incidence of cardiovascular morbidity. Data from the Framingham Study have demonstrated that the mean aortic pressure and diastolic blood pressure measurements significantly underestimate peripheral vascular resistance and the risk of coronary heart disease [14]. Additionally, while changes in systolic blood pressure were determined to reflect peripheral vascular resistance, the risk of coronary heart disease was frequently underestimated. The use of pulse pressure measurements was demonstrated to be superior to systolic blood pressure as a surrogate marker for arterial stiffness, and also to be predictive of coronary heart disease. Observational studies have demonstrated in men and older subjects that any level of systolic blood pressure in excess of 120 mg per deciliter was correlated with an increased risk for the development of a cardiovascular event, and the risk rose discordantly with lowered diastolic blood pressure. The observational data suggested that a wide pulse pressure is a major driving force for the risk of coronary heart disease [15]. The measurement of pulse pressure in the brachial artery as a surrogate marker for arterial stiffness and a means to predict cardiovascular events is attractive due to simplicity both in the ease of measurement and accuracy. However, the reflected pressure waves generated from peripheral arteries demonstrate the largest amplitude at their origin, and increasing distance from the heart results in an increase both in the pulse pressure and systolic pressures, which correlates with the distance from the heart. The central circulation, which is composed of the aortic and carotid pressures, demonstrates a higher degree of clinical relevance when compared to peripheral pressure measurements, when considering the risk for the development and progression of vascular disease [16]. Clinical studies have demonstrated that the brachial and central blood pressure measurements mat vary by as much as 20 mm of mercury, which has significant physiologic implications [17] The determination of aortic pulse pressure has been demonstrated to be predictive of the development of subsequent cardiac events. Clinical studies have demonstrated that the measurement of aortic pulse pressure appears to be an independent marker of cardiovascular risk in elderly subjects and end-stage renal disease [18].

Pulse Wave Velocity

Following ventricular systole, the pressure generated by the heart is transmitted to the aorta as a wave. The pulse wave velocity is simply the time required for the pressure wave to travel between two regions in the arterial tree. The rapidity of the transmission of the pressure wave is increased in stiffer vessels. Quantification of the velocity of the pulse wave is considered to be the most useful clinical marker of arterial stiffness [2]. The pulse wave velocity has been demonstrated to be a useful and independent predictor of cardiovascular events when controlled for concomitant risk factors, and also demonstrates considerable predictive values in the elderly [19, 20] . The pulse wave velocity is relatively easily quantitated, but is influenced by a variety of factors, including vascular dimensions that modify the readings and render the determination of pulse wave velocity to be an indirect marker of vascular stiffness. The quantitation of pulse wave velocity requires the placement of serial transducers over the arterial bed. The pulse wave velocity is measured by quantitation of the distance between the transducers and dividing by the time required for the wave to appear at the second transducer. The pulse wave velocity is directly correlated with the precise distance between the measuring transducers. However, the magnitude of pulse wave velocity may also be altered by a variety of physiologic parameters [21]. Clinical studies have clearly demonstrated a strong positive relationship between pulse wave velocity and hypertension. However, positive (although variable in magnitude) associations have been demonstrated between pulse wave velocity and age, heart rate, body mass index, hematocrit and blood glucose. Additionally, structural and physiologic alterations of the artery including baseline vascular tone, thickening of the medial smooth muscle, and modification of blood viscosity have all been demonstrated to alter the degree of pulse wave velocity. However, meta-analysis has demonstrated that age and blood pressure were consistently and independently associated with pulse wave velocity, and indicated that the contribution of risk factors other than hypertension and the aging process is insignificant [22].

The normal pulse wave velocity is 10 m/s in individuals 60–65 years of age. Clinical studies have demonstrated that quantitation of aortic pulse wave velocity has been widely validated as providing additional prognostic information above and beyond standard cardiovascular risk stratification [23, 24]. Pulse wave velocity increases with the aging process, and has been demonstrated to be a significant predictor of cardiac events in elderly individuals. Pulse wave velocity in the aorta has been determined to be an independent risk factor for cardiac events. A meta-analysis of studies analyzing pulse wave velocity was performed, and was compromised of 17 longitudinal studies that evaluated 15,877 subjects over a mean period of 7.7 years. The analysis determined that the pooled relative risk for the development of significant cardiovascular events was linearly related from the first to the third tertile of aortic pulse wave velocity. All-cause mortality demonstrated a 1.9 relative risk (95 % confidence interval 1.61 to 2.24) for high versus low aortic pulse wave velocity. Additionally, an increase in aortic pulse wave velocity by 1 m/s demonstrated a risk factor adjusted risk increase of 15 %. Aortic stiffness has been demonstrated to be a strong predictor of the subsequent risk for the development of cardiac events and all-cause mortality. Increased cardiovascular risk factor clustering is associated with a higher predictive value [25].

Augmentation Index

The determination of the augmentation index is a readily available means to estimate the degree of arterial stiffness. The large conduit arteries exhibit considerable compliance, which allows acceptance of the cardiac output with a cushioning effect that damps pressure within the arterial system and directs the cardiac output into the peripheral vessels with relatively laminar flow. Additionally, the large conduit vessels absorb the oscillations generated in the periphery, which are reflected retrograde. The magnitude of the reflected wave is a function of vascular function and structural components. Hence, the summation of the reflected pressure waves from the periphery with the antegrade pressure determines the observed waveform at any point within the arterial system. Progressive arterial stiffening results in an increase of transmission velocity of the forward wave generated during myocardial systole and the reflected wave, which returns from the peripheral resistance vessels. The increased rate of transmission of the retrograde pressure wave results in the earlier arrival in the central circulation and a secondary increase or augmentation of pressure that occurs late in the systolic phase. The augmentation index is the augmented pressure/pulse pressure. Recordings of the pressure waveforms demonstrate the oscillations and provide the basis for determination of the augmentation index. The augmentation index represents the merger of the waveform propagated during systole with the reflected waves from the peripheral vessels. The central arterial pressure wave has several components (Pi or inflection wave, Ps or systolic wave, and Pd or minimum diastolic wave). The total pressure in the central aortic has an amplitude of Ps – Pd, and is composed of a forward traveling wave with an amplitude of Pi-Pd and a reflected wave that returns later in the cycle and is measured as Ps-Pi. The amplitude of the forward wave is a function of mechanical properties of the major elastic vessels in the central circulation. The forward wave is not modified by reflections of pressure waves from peripheral vessels. However, the elastic properties of the total circulation, which include the elastic and muscular vessels, exhibit considerable influence upon the reflected waves. The

augmentation index is a calculation that measures the height of the reflected wave relative to the incident wave and is a measure of arterial stiffness. Thus, the augmentation index (AI) is equal to the (Ps-Pi) – (Ps-Pd). Early studies that analyze the augmentation index and potential modifying factors required direct pressure measurements obtained from invasive catheter based techniques that were not practical in clinical practice. However, advances in technology have provided a variety of noninvasive methods to measure augmentation index. Pressure phenomenon in the radial artery can be quantitated and coupled with calculations of the pressures within the ascending aorta, utilizing a mathematical transfer function. Multiple clinical studies have been performed and have validated the methods [26, 27]. However, a variety of multiple factors influence the calculations, which must be taken into account when applying the results of noninvasive testing utilizing these methods as a quantitative indicator of aortic stiffness. Multiple clinical parameters exhibit significant effects on the results including the heart rate, gender and height [28]. Clinical studies have demonstrated that older women have a tendency to exhibit parameters compatible with stiffer arteries when compared to age-matched male subjects. The mechanism is unclear, but is presumably secondary to hormonal changes. Additionally, the aging process and elevated blood pressure are associated with increases in arterial stiffness [29]. Pathologic alterations in the arterial wall associated with progressive stiffness are well documented. The loss of elastic fibers is a significant contributor to arterial stiffness and increases with age. The elastic fibers undergo progressive fragmentation with a resultant alteration of their physiologic function. The pathologic changes associated with the elastic fibers are compounded by an increase in collagen deposition, which significantly increases arterial stiffness. Additionally, metabolic disorders such as diabetes mellitus have been demonstrated to alter the augmentation index. Cardiovascular mortality is significantly increased in diabetic subjects due to multiple metabolic arrangements. The vascular dysfunction associated with diabetes mellitus is manifest as an increase in arterial stiffness. Central hemodynamics in diabetic subjects have been evaluated utilizing nondiabetic individuals with similar mean aortic pressures [30]. The pulse-wave velocity and augmentation index were demonstrated to be significantly increased in diabetic subjects following adjustment for age, gender, and heart rate in mean aortic pressure. However, following further adjustment for the presence of the metabolic syndrome, only the difference in pulse-wave velocity persisted. Diabetic subjects manifest multiple factors that may be adverse to arterial stiffness independent of the hemodynamic parameters. The utilization of insulin therapy has been demonstrated to be associated with more severe indices of aortic stiffness, although direct causal effects remained to be determined.

Arterial Stiffness and Cardiovascular Risk

The measurement of arterial stiffness has been significantly refined and can be performed in an accurate and reproducible manner. It has been proposed to be incorporated in risk prediction protocols and classified as an emerging cardiovascular risk factor. However, markers of arterial stiffness are interrelated with a variety of hemodynamic parameters, such as measurements of blood pressure including heart rate systolic, diastolic and pulse pressure. The interrelationship of these various parameters are difficult to separate on clinical grounds, which renders the study of the individual impact of various interventions on clinical outcome to be problematic, as various therapies have overlapping outcomes on modification of stiffness and hemodynamics [31, 32]. The Framingham Heart Study has utilized a proportional hazards model to analyze the effect of arterial stiffness on the risk for the development of an initial cardiac event [33]. The application of techniques that measure aortic pulse-wave velocity were employed as a means to predict the development of cardiac events following adjustment for gender, systolic blood pressure, lipid profiles, antihypertensive medication, smoking and diabetes mellitus. Documentation of an elevated pulse-wave velocity was associated with a 48 % relative risk increase in cardiovascular events (95 % confidence interval 1.16–1.91), which was highly statistically significant. In contrast to other clinical observations, this study demonstrated that augmentation index, central pulse pressure and pulse pressure amplification were not related to cardiovascular outcomes when evaluated employing multivariate analysis. However, controversy has arisen relative to the cause and effect relationship between hypertension and aortic stiffness. The prevailing consensus has been that hypertension developed and subsequently damaged the aorta due to increase physical stress and resulted in aortic stiffness [34]. However, recent studies from the Framingham Heart Study have implicated that aortic stiffness precedes hypertension, and progressive structural and functional changes in the aorta may exist prior to the development of increased levels of blood pressure [35••]. The observational study was conducted in a longitudinal fashion and demonstrated that an increase in forward wave amplitude, augmentation index and higher aortic stiffness was demonstrated to be associated with a significantly increased risk for the development of hypertension in previously normotensive individuals. However, initial blood pressure readings were not independently associated with the subsequent development of elevated blood pressure.

Multiple pharmacologic agents have been proposed to modify arterial stiffness, and have focused predominantly on antihypertensive agents [36]. Pharmacologic agents have been demonstrated to exhibit properties other than blood pressure lowering, which has rendered the precise mechanism by which the administration of antihypertensive medications

impacts upon cardiovascular mortality to be problematic [37]. In the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA), a total of 19,257 hypertensive individuals were randomized to one of two treatment arms. Amlodipine plus perindopril was compared to standard therapy, which included the cardioselective beta blocker atenolol plus diuretic therapy in a prospective controlled randomized trial design. The administration of amlodipine plus perindopril was significantly more efficacious in the reduction of cardiovascular events than standard therapy, despite relatively equal modification of blood pressure. The results of this trial implied that clinical benefit may be related to factors independent of blood pressure modification as measured by brachial sphygmomanometry. A subset of the Ascot trial was analyzed to potentially provide insight into the mechanism of cardiovascular benefit. The Conduit Artery Function Evaluation (CAFÉ) trial analyzed 2,199 subjects enrolled in the ASCOT study with determination of arterial stiffness and central aortic pressure. The results of the CAFÉ study demonstrated that the amlodipine-based regimen was significantly more efficacious in the reduction of central aortic systolic, diastolic and pulse pressure and augmentation index. Further analysis of the data implicated that the reduction of heart rate induced by beta blockade may play a significant role in the less-than-optimal effect of atenolol-based therapy on central pressure measurements [38]. Brachial systolic or pulse pressure was not affected by reductions in heart rate induced by atenolol. However, a strong inverse relationship between heart rate and central aortic systolic and pulse pressures was documented. Potential mechanisms include the fact that reduction of the heart rate does prolong the cardiac ejection time but has no effect on pulse wave velocity, which would result in the reflected wave arriving later in systole. The reduction of dP/dT associated with beta blocker therapy during systole could delay the time to the peak of the outgoing wave.

Summary

The traditional view of the arterial system as a passive conduit has been challenged over the past several decades, due to significant advances in the delineation of the role of endothelial function and the impact of a variety of pathophysiologic factors on arterial structure and function. The concept of arterial stiffness and measurements of quantitative parameters have significantly advanced the role of the vascular system, and had been classified as an emerging risk factor for the development of coronary artery disease. The role of the pulse pleasure as a predictor of cardiac events has been significantly expanded by the utilization of the augmentation index and determination of pulse-wave velocity as a means to evaluate the structural and functional aspects of the arterial system. The utilization of these parameters extended the understanding of antihypertensive therapy and clarified mechanisms underlying clinical trials that demonstrated differing impact upon clinical outcomes, despite similar reductions in blood pressure as measured by brachial sphygmomanometry. Further research will be required to establish the clinical role of more widespread implementation of measures of arterial stiffness to establish prognosis in cardiovascular disease and provide a basis for intensity of therapy.

Conflict of Interest Josh Liao and John A. Farmer declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Hopkins PN. Molecular biology of atherosclerosis. Physiol Rev. 2013;93(3):1317–542. Excellent overview of the basic science pathways involved in the initiation and progression of atherosclerosis. The paper discusses the molecular basis of the pathologic changes in the vascular system that result in the long-term development of loss of arterial compliance.
2. Safar ME. Arterial aging–hemodynamic changes and therapeutic options. Nat Rev Cardiol. 2010;7(8):442–9.
3. Langille BL. Remodeling of developing and mature arteries: endothelium, smooth muscle, and matrix. J Cardiovasc Pharmacol. 1993;21 Suppl 1:S11–7.
4. • Gauthier-Bastien, A., et al. *Vascular remodeling and media calcification increases arterial stiffness in chronic kidney disease.* Clin Exp Hypertens, 2013. Overview of the maladaptive remodeling process that delineates the pathologic processes in the histologic changes within the vasculature resulting in arterial stiffness.
5. London GM, Cohn JN. Prognostic application of arterial stiffness: task forces. Am J Hypertens. 2002;15(8):754–8.
6. de Souza F, Muxfeldt ES, Salles GF. Prognostic factors in resistant hypertension: implications for cardiovascular risk stratification and therapeutic management. Expert Rev Cardiovasc Ther. 2012;10(6):735–45.
7. Raij L, Gonzalez-Ochoa AM. Vascular compliance in blood pressure. Curr Opin Nephrol Hypertens. 2011;20(5):457–64.
8. Nichols WW. Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. Am J Hypertens. 2005;18(1 Pt 2):3S–10S.
9. O'Rourke MF, Kelly RP. Wave reflection in the systemic circulation and its implications in ventricular function. J Hypertens. 1993;11(4):327–37.
10. O'Rourke MF, Nichols WW. Aortic diameter, aortic stiffness, and wave reflection increase with age and isolated systolic hypertension. Hypertension. 2005;45(4):652–8.
11. Yildiz O. Vascular smooth muscle and endothelial functions in aging. Ann N Y Acad Sci. 2007;1100:353–60.

12. Franklin SS et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation. 1997;96(1):308–15.
13.• Chirinos JA. Arterial stiffness: basic concepts and measurement techniques. J Cardiovasc Transl Res. 2012;5(3):243–55. Basic science overview of the principles involved in the measurement of arterial stiffness modification.
14. Mendis S. The contribution of the Framingham Heart Study to the prevention of cardiovascular disease: a global perspective. Prog Cardiovasc Dis. 2010;53(1):10–4.
15. Franklin SS. Ageing and hypertension: the assessment of blood pressure indices in predicting coronary heart disease. J Hypertens Suppl. 1999;17(5):S29–36.
16. Agabiti-Rosei E et al. Central blood pressure measurements and antihypertensive therapy: a consensus document. Hypertension. 2007;50(1):154–60.
17. Wilkinson IB et al. The influence of heart rate on augmentation index and central arterial pressure in humans. J Physiol. 2000;525(Pt 1):263–70.
18. Safar ME et al. Central pulse pressure and mortality in end-stage renal disease. Hypertension. 2002;39(3):735–8.
19. Blacher J et al. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension. 1999;33(5):1111–7.
20. Meaume S et al. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. Arterioscler Thromb Vasc Biol. 2001;21(12):2046–50.
21. Taquet A et al. Relations of cardiovascular risk factors to aortic pulse wave velocity in asymptomatic middle-aged women. Eur J Epidemiol. 1993;9(3):298–306.
22. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. Hypertension. 2009;54(6):1328–36.
23. Boutouyrie P et al. Cardiovascular risk assessment through target organ damage: role of carotid to femoral pulse wave velocity. Clin Exp Pharmacol Physiol. 2008;35(4):530–3.
24. Zoungas S, Asmar RP. Arterial stiffness and cardiovascular outcome. Clin Exp Pharmacol Physiol. 2007;34(7):647–51.
25. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;55(13):1318–27.
26. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension. 2001;38(4):932–7.
27. Chen CH et al. Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure. Hypertension. 1996;27(2):168–75.
28. Gatzka CD et al. Correction of carotid augmentation index for heart rate in elderly essential hypertensives. ANBP2 Investigators. Australian Comparative Outcome Trial of Angiotensin-Converting Enzyme Inhibitor- and Diuretic-Based Treatment of Hypertension in the Elderly. Am J Hypertens. 2001;14(6 Pt 1):573–7.
29. Nichols WW, Singh BM. Augmentation index as a measure of peripheral vascular disease state. Curr Opin Cardiol. 2002;17(5):543–51.
30. Agnoletti D et al. Central hemodynamic modifications in diabetes mellitus. Atherosclerosis. 2013;230(2):315–21.
31. Domanski MJ et al. Isolated systolic hypertension : prognostic information provided by pulse pressure. Hypertension. 1999;34(3):375–80.
32. Franklin SS et al. Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study. Circulation. 1999;100(4):354–60.
33. Mitchell GF et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation. 2010;121(4):505–11.
34. Aatola H et al. Lifetime risk factors and arterial pulse wave velocity in adulthood: the cardiovascular risk in young Finns study. Hypertension. 2010;55(3):806–11.
35.•• Kaess BM et al. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA. 2012;308(9):875–81. Excellent paper providing clinical evidence that measurements of arterial stiffness and endothelial function serve as a harbinger of essential hypertension in individuals who are initially normotensive.
36. Dudenbostel T, Glasser SP. Effects of antihypertensive drugs on arterial stiffness. Cardiol Rev. 2012;20(5):259–63.
37. Poulter NR et al. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). Lancet. 2005;366(9489):907–13.
38. Williams B, Lacy PS. Impact of heart rate on central aortic pressures and hemodynamics: analysis from the CAFE (Conduit Artery Function Evaluation) study: CAFE-Heart Rate. J Am Coll Cardiol. 2009;54(8):705–13.