

VASCULAR COMPLIANCE: METHODS OF ASSESSMENT AND CLINICAL SIGNIFICANCE

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REZUMAT

Scăderea complianței vasculare cu vârsta este unul din factorii ce contribuie la apariția hipertensiunii sistolice izolate la vârstnici. Pe lângă aceasta însă, scăderea complianței arterelor mari este un factor de prognostic independent și care se asociază frecvent cu alți factori de risc cardiovascular. Determinarea gradului de rigiditate arterială prin metode neinvazive a câștigat tot mai multă atenție în ultimii ani. Dintre aceste metode, cele mai utilizate sunt măsurarea vitezei undei pulsatile, corelarea modificării diametrului vascular cu presiunea de distensie și analiza conturului undelor sistolice și diastolice. Dintre acestea, determinarea vitezei undei pulsatile, un indicator clasic de rigiditate aortică, pare să fie metoda cea mai utilă de diagnostic și prognostic pentru scăderea complianței arteriale. Evaluarea gradului de rigiditate arterială ar putea reprezenta unul din markerii de risc cardiovascular atât la pacienții hipertensivi, cât și la cei normotensivi dar cu cumul de factori de risc, independent de vârstă, tensiunea arterială sau masa ventriculară.

Cuvinte cheie: complianță vasculară, evaluare noninvazivă, prognostic

ABSTRACT

The decrease of vascular compliance with aging represents one of the factors involved in the occurrence of isolated systolic hypertension in the elderly. Beside this, large arteries alteration of compliance is an independent prognostic factor, frequently associated with other cardiovascular risk factors. The assessment of the degree of arterial stiffness by noninvasive methods has gathered much attention in the recent years. Among these methods, the most used are the measurement of pulse wave velocity, relating change in vessel diameter to distending pressure and systolic and diastolic pulse contour analysis. From these methods, pulse wave velocity measurement, a classic index of aortic stiffness, seems to be the most useful diagnostic and prognostic method of arterial compliance alteration. The assessment of arterial stiffness could represent one of the cardiovascular risk markers in hypertensive, but also in normotensive patients with more risk factors, independent of age, blood pressure or ventricular mass.

Key Words: arterial compliance, noninvasive assessment, prognosis

INTRODUCTION

The association between blood pressure (BP) and major cardiovascular events is now well established. This association has a linear relationship with the increase in BP values and is greatly influenced by age. Many trials have shown a positive association between systolic and pulse pressure and cardiovascular events.

Because systolic, diastolic and pulse pressure are related to the physical properties of elastic arteries, interest has been directed toward arterial stiffness, pulse wave velocity and wave reflections as cardiovascular risk factors. This paper presents some hemodynamic considerations concerning arterial compliance, the methods of assessing it and the prognostic role of each parameter of arterial stiffness.

HEMODYNAMIC CONSIDERATIONS

The circulation is a central elastic reservoir (the large arteries), into which the heart pumps, and from which blood travels to the tissues through relatively non-elastic conduits (peripheral arteries). The elasticity of the proximal large arteries is the result of the high elastin to collagen ratio in their walls, which progressively declines toward the periphery. The increase in arterial stiffness that occurs with age is largely the result of

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progressive elastic fiber degeneration.¹ The principal changes with age occur in the intima, which undergoes hyperplasia, and the media. In the arterial media, the elastic fibers and laminae lose the orderly arrangement and display thinning, splitting and fragmentation. The age-related thinning and fragmentation of elastin and the increase in collagen are not seen in the muscular arteries. Collagen in the human aorta is much stiffer than elastin and it doubles in content from age 20 to 70 years.

The elasticity of a given arterial segment is not constant but instead depends on its distending pressure. As distending pressure increases, there is greater recruitment of relatively inelastic collagen fibers and, consequently, a reduction in elasticity.² The background level of distending pressure in the circulation is determined by the mean arterial pressure (MAP). This is important because MAP must be taken into account whenever measurements of arterial stiffness are made so that anticipated effects of distending pressure can be differentiated from real differences in the elasticity of the arterial wall. In addition to collagen and elastin, the endothelium and arterial wall smooth muscle bulk and tone (the latter under some control from the endothelium) also influence elasticity.²⁻⁵

A number of genetic influences on arterial stiffness have also been identified. Thus, polymorphic variation in the fibrillin-1, angiotensin II type-1 receptor and endothelin receptor genes are related to stiffness.⁶⁻⁸ The angiotensin converting enzyme (ACE) I/D polymorphism has been associated with stiffness, but not consistently.⁷

Ejection of blood from the left ventricle during systole initiates an arterial pressure wave that travels toward the periphery. As the pressure wave travels from the heart to the periphery, both systolic and pulse pressures increase, whereas diastolic and mean pressures decrease only slightly due to progressive increase in arterial stiffness and to the cumulated effects of incident and reflected waves. Thus, both systolic and pulse pressures are greater in the arm and leg than in the ascending aorta. The degree of amplification is related to differences between the elasticity of the arteries and to the distance between the reflection sites. Therefore, brachial cuff blood pressure is not always a reliable measure of ascending aortic pressure and thus is not always a good predictor of left ventricular afterload and mass.

Recent studies have shown central artery pulse pressure to be a better predictor of coronary artery severity, mortality in end-stage renal disease and restenosis after coronary angioplasty.⁹⁻¹¹

During systole, the contraction of left ventricular myocardium and the ejection of blood into the ascending aorta acutely dilate the aortic wall and generate a pulse wave that propagates along the arterial tree at a finite speed. This propagation velocity constitutes an index of arterial distensibility and stiffness: the higher the velocity, the higher the rigidity of the vascular wall and the lower the distensibility.

The pressure pulse generated by ventricular ejection is propagated throughout the arterial tree at a speed that is determined by the elastic and geometric properties of the arterial wall and the characteristics (density) of the contained fluid (blood). Since blood is an incompressible fluid and is contained in elastic conduits (arteries), the energy propagation occurs predominantly along the walls of the arteries and not through the incompressible blood. Thus, the properties of the arterial wall, its thickness, and the arterial lumen diameter are the major factors influencing pulse wave velocity (PWV). The relationships between PWV, transmural pressure, wall tension and distensibility have been formalized in many mathematic models. The contour and amplitude of the pressure waveform are influenced by large artery PWV, in that faster traveling pressure waves arrive at, and are reflected from, the peripheral circulation earlier.

When arteries are relatively compliant and PWV is relatively slow, reflected waves return to the central aorta in diastole, augmenting DBP and, therefore, coronary blood flow, which occurs predominantly during diastole. When arteries are stiffer and PWV is higher, reflected waves arrive earlier and augment central SBP, rather than DBP, increasing left ventricular workload and compromising coronary blood flow.^{12,13}

NON-INVASIVE ASSESSMENT OF ARTERIAL STIFFNESS

Many methodologies, both invasive and noninvasive, have been applied to the assessment of arterial elasticity *in vivo*. The noninvasive methods of assessment include: measuring PWV, relating change in diameter (or area) of an artery to the distending pressure, and assessing arterial pulse contour.

Pulse Wave Velocity (PWV)

Among the noninvasive and simple methods of evaluating arteries, PWV measurement is widely used as an index of large artery elasticity and stiffness. This method is simple, accurate and reproducible and thus can easily be applied for the evaluation of the cardiovascular risk.

There are a number of different ways to measure PWV, and these are generally simple to perform. Since the aorta is the major component of arterial elasticity, the carotid-femoral PWV offers the simplest reproducible and noninvasive evaluation of regional stiffness. The arterial pulse wave is recorded at a proximal artery, such as the common carotid, as well as at a more distal artery, such as the femoral. The superficial location of the carotid and femoral arteries means that their pulse waveforms are readily measured noninvasively, and between these two sites the pulse wave has to travel through most of the aorta, an artery particularly prone to the development of atherosclerosis. The time delay between the arrivals of a predefined part of the pulse wave, such as the foot, at these 2 points is obtained either by simultaneous measurement, or by gating to the peak of the R-wave of the ECG. The distance traveled by the pulse wave is measured over the body surface and PWV is then calculated as distance/time (m/s). The measured distance is an estimate of the true distance traveled and depends to some extent on body habitus. An accurate measurement of this distance is obtained only with invasive procedures. Therefore some authors suggest, for noninvasive measurement, a possible correction based on anatomic dimensions of the body. Others recommend subtracting the distance between the suprasternal notch to the carotid location from the total distance when the carotid pulse pressure is recorded instead of the aortic arch pulse. Furthermore, the abdominal aorta tends to become more tortuous with age, potentially leading to an underestimation of PWV.¹⁴

Arterial pulse waves can be detected by using pressure-sensitive transducers, Doppler ultrasound (the pressure pulse and the flow pulse propagate at the same velocity) or applanation tonometry where the pressure within a small micromanometer flattened against an artery equates to the pressure within the artery.¹⁵⁻¹⁷

Aortic PWV can also be measured noninvasively by using MRI.¹⁸ MRI has the potential advantage of accurate determination of path length, although factors, such as the time required to make a recording, lack of availability in the immediate clinical setting, relatively high cost per measurement, and the difficulty in performing clinical studies within a strong magnetic field, mean that few studies have been performed with this technique. However, a recent study showed that MRI offers insights not otherwise possible, in describing greater age-related increase in PWV in the proximal than in the distal aorta.¹⁹

Increases in distending pressure increase PWV.

Therefore, account should be taken of the level of BP in studies that use PWV as a marker of cardiovascular risk or as a measure of the effects on arterial stiffness of interventions that reduce BP. Heart rate has also been reported to influence PWV. In one study an increase in heart rate of 40 beats per minute increased PWV by > 1 m/s a difference that may be relevant to the assessment of cardiovascular risk.²⁰ Elevated heart rate was significantly associated with low arterial compliance and high PWV, even after adjusting for age and BP. The most significant correlations between high heart rate and high PWV were found at the site of elastic arteries such as the thoracic aorta and the carotid artery, but not in the muscular arteries. Another factor that influences PWV is age: the higher the age, the higher the aortic PWV. Above 70 years aortic PWV is exclusively influenced by blood pressure, but not by age.²¹

Relating Change in Vessel Diameter (or Area) to Distending Pressure

The change in diameter of a number of arteries, such as the carotid, brachial, radial, and aorta, can be related to the distending pressure, providing a series of direct measures of stiffness. Ultrasound is the most frequently used imaging modality, although MRI has been used rarely. Calculation of parameters, such as compliance and distensibility, requires that the incremental pressure of the artery in question be known, for example, the carotid pulse pressure. Alternatively, applanation tonometry can be used to assess carotid BP. Although this technique is not normally used to measure absolute pressure, the brachial artery mean arterial pressure can be assumed to be equal to that in the carotid so that the absolute pressure of the carotid waveform can be calculated.

An alternative approach proposed to characterize the elastic properties of arteries independently of distending pressure is to calculate the stiffness index.

Pressure–diameter relationships can be accurately determined invasively with simultaneous measurement of arterial pressure by using a luminal pressure transducer and dimensions by using intravascular ultrasound. In a similar manner to the noninvasive methods, this technique can differentiate the effects on elasticity of distending pressure from the intrinsic properties of the vessel wall. The use of this technique in reducing aortic distensibility has been demonstrated with increased age, in patients with coronary heart disease, hypertension and hypercholesterolemia, and acutely after smoking.^{22,23} This technology has not been applied to the carotid artery, although such

studies would help to determine the reliability of the non-invasive techniques.

MRI can also be used to measure noninvasively the arterial, usually aortic, distensibility, although its value is probably limited to small mechanistic studies. In healthy subjects MRI revealed compliance to be greater in the ascending aorta than the aortic arch where, in turn, it was greater than in the proximal descending aorta.

Aortic compliance was greater in athletes and lower in patients with coronary heart disease compared with matched controls.²⁴ Aortic distensibility was reduced in hypertensive subjects, whether measured at the ascending, descending thoracic or abdominal aorta, but differences in distending pressure were not accounted for in either of these studies.

Pulse contour analysis

Systolic Pulse Contour Analysis (SPCA)

Analyses of specific components of the arterial pressure or flow waveform are used by a number of noninvasive methodologies designed to measure arterial stiffness. Peripheral artery pressure waveforms can be acquired noninvasively by using applanation tonometry. SPCA uses a transfer function to derive central aortic waveforms from those obtained from a peripheral artery, most commonly the radial artery.

From the central aortic waveform central BP values and the augmentation index (AIx) can be calculated. The AIx is the proportion of central pulse pressure that results from arterial wave reflection and is a commonly used to measure of arterial stiffness. Increased arterial stiffness increases PWV and causes early return of the reflected wave from peripheral reflecting sites to the heart during systole when the ventricle is still ejecting blood. This mechanism increases aortic systolic and pulse pressures, having as consequences increases in arterial wall stress, left ventricular afterload and mass, and decrease of the stroke volume.²⁵

Although the timing of the arrival of the reflected wave at the proximal aorta is largely determined by large artery PWV, AIx is not simply a surrogate measure of PWV. It is influenced by vasoactive drugs independently of PWV, suggesting that it is also determined by the intensity of wave reflection, the latter being determined by the diameter and elasticity of small arteries and arterioles.²⁶ AIx increases with mean arterial pressure and is inversely related to heart rate and body height, so these variables should be accounted for when interpreting studies that use SPCA. SPCA is simple, rapid, and can be used in the clinical as well as research setting.

Diastolic Pulse Contour Analysis (DPCA)

The analysis of the diastolic portion of the pressure pulse contour can be used to derive information on the compliance of both proximal and distal arteries. As with SPCA, the waveform of the radial artery can be determined noninvasively by using tonometry and calibrated for BP by using standard sphygmomanometry, potentially allowing for wide clinical application. Values obtained by using the noninvasive methodology have been compared with those obtained from waveforms obtained invasively.²⁷ Tonometry-measured pressure tended to underestimation, but was tightly correlated to pressure determined invasively.

Assessment of arterial compliance by using DPCA has been applied to a number of at-risk populations. Using both brachial artery waveforms obtained invasively and radial artery waveforms obtained noninvasively with tonometry, increased age was associated with reduced large and small artery compliance, whether assessed invasively or noninvasively.²⁸ Although the relationship between age and large artery compliance was similar however measured, the decline in small vessel compliance was greater when measured noninvasively. SBP was independently associated with reduced large artery compliance, but small artery compliance was not associated with any BP parameter. DPCA has been proposed as a sensitive marker of early vascular disease. However, several deficiencies of the technique used, the probable influence of the regional circulatory properties (arterial length, number of reflection sites, stiffness of individual arteries) raise doubts concerning the use of this methodology in accurately determining arterial compliance.

PROGNOSTIC VALUE

Raised PWV occurs with a range of established cardiovascular risk factors, including age, hypercholesterolemia, type 2 diabetes, and sedentary lifestyle.²⁹⁻³¹ Moreover, some studies have found an inverse relationship between the number of risk factors and aortic compliance determined noninvasively on the basis of aortic PWV.³²

In hypertension, carotid-femoral PWV is an independent predictor of both cardiovascular and all-cause mortality.³³ The odds ratio for a 5 m/s increment in PWV was 1.34 for all-cause mortality and 1.51 for cardiovascular mortality. In contrast, pulse pressure was independently related to all-cause mortality but only marginally related to cardiovascular mortality, indicating that specific assessment of arterial stiffness,

with PWV, may be of greater value in the evaluation of risk. It should be noted that 5 m/s is a relatively large change in PWV. In this study PWV ranged from 9 to 13 m/s, whereas recently quoted values of carotid–femoral PWV in healthy individuals with average ages of 24 to 62 years ranged from around 6 to 10 m/s.³⁴ Differences between studies regarding the method used to calculate the distance traveled between the carotid and femoral sites probably explains some of the variation in these normal values.

In hypertensives without a history of overt cardiovascular disease PWV also predicts the occurrence of cardiovascular events independently of classic risk factors. Aortic PWV >13 m/s is a particularly strong predictor of cardiovascular mortality in hypertension.³⁵ Recently published data show that carotid–femoral PWV increases at a faster rate in treated hypertensives than in normotensive controls, although where BP was well controlled PWV progression was attenuated.³⁶ High heart rate and plasma creatinine >8 mg/L were other determinants of accelerated progression of PWV in hypertensives in this study. Aortic PWV, assessed by using Doppler flow recordings, also independently predicts mortality in patients with end-stage renal failure, a population with a particularly high rate of cardiovascular disease.³⁷ The benefit associated with BP control in end-stage renal failure, either by adjustment of dry weight or the use of antihypertensives, was independently related to change in aortic PWV, such that a reduction in PWV of 1 m/s was associated with a relative risk of 0.71 for all-cause mortality.³⁸

SPCA has been used to explain why peripheral diastolic BP is a better predictor of coronary heart disease risk in the young, while in the elderly the strongest predictor of risk is peripheral pulse pressure. In young subjects, as diastolic BP increases early wave reflection also increases, producing a reduction in peripheral pulse pressure amplification. In the elderly, this amplification does not depend on the diastolic BP, because wave reflection is already increased due to arterial stiffening.

AIx increases with age and, compared with matched controls, is also higher in patients with type 1 diabetes and hypercholesterolemia, despite similar peripheral BP.³⁹⁻⁴⁰ Thus far, there are no data on the prognostic value of AIx calculated from the central aortic waveform when derived from radial artery tonometry. However, SPCA has been incorporated into a number of prospective cohort studies with hard clinical endpoints, including the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) in hypertensives, the Edinburgh Artery Study in atherosclerosis, the

Study of the Effectiveness of Additional Reduction in Cholesterol and Homocysteine with Simvastatin and Folic Acid/Vitamin B12 (SEARCH), and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study.

High carotid Aix is an independent predictor both of cardiac ischemic threshold during exercise in patients with coronary heart disease and of all-cause and cardiovascular mortality in patients with end-stage renal failure.^{41,42} Of particular note from the latter study, AIx predicted mortality even in patients considered to have a normal PWV (<11 m/s), highlighting the importance of assessing arterial wave reflection, rather than just arterial stiffness.

CONCLUSIONS

There is a need for a simple, reliable, noninvasive method of detecting early disturbances in arterial compliance at a time when therapeutic intervention can be most beneficial. Currently, none of the methodologies available are suitable for widespread use in clinical practice. Arterial waveform analysis by using tonometry of the radial artery requires minimal training and can be rapidly measured. In contrast, PWV and ultrasonography are more time consuming and ultrasonography in particular requires substantial training. However, PWV measurement can be done with validated automatic devices with minimal training. With regard to the prognostic value, currently the most characterized of the measured parameters is aortic PWV. Therefore, noninvasive determination of aortic PWV can be a useful index of arterial compliance and can help evaluating the risk of the patients with or without arterial hypertension but with other classical risk factors.

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