**Arterial Stiffness and Hypertension**

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**OVERVIEW OF THE ROLE OF ARTERIAL STIFFNESS IN HYPERTENSION**

Historically, arteries were considered to be passive conduits of blood; today, they are viewed as complex, active participants in cardiovascular function, including abnormalities in blood pressure. Stiffening of large arteries may be both a cause and a consequence of hypertension. There are several studies, including studies done by the University of Minnesota, that confirm that as arterial pressure rises, acute and reversible stiffening of the large arteries occurs without a change in the structure of the artery. Arterial stiffness increases transiently as blood pressure rises. Arterial stiffening also increases because of the structure of the artery changes. Persistently elevated blood pressure accelerates atherosclerosis, arterial smooth muscle hyperplasia and hypertrophy, and collagen synthesis, thereby increasing arterial stiffness. (Fig. 1)

![The Arterial Wall](image)

Different arteries have different ratios of arterial wall structural components. Hypertension causes medial hypertrophy, elastin degradation, and collagen formation.

- **Intima**
  - endothelium
  - connective tissue

- **Media**
  - smooth muscle
  - protein matrix of elastin/collagen
  - internal elastic lamina

- **Adventitia**
  - strong, fibrous tissue to maintain vessel shape

**Modified from:**

Both transient and sustained stiffening of the artery are likely to be present in hypertension. An initial elevation in blood pressure may establish a positive feedback in which hypertension biomechanically increases arterial stiffness without any structural change. This elevated blood pressure might later lead to additional vascular hypertrophy and hyperplasia, collagen deposition, and atherosclerosis, and fixed
Arteries cushion the cardiac pulsation, converting intermittent blood flow to steady flow. During systole, the aorta expands to accommodate flow (the stroke volume) and recoils during diastole to promote forward flow. Since the aorta has a limited capacity, pressure increases during systole (systolic blood pressure) and is partially maintained during diastole (diastolic blood pressure) by the rebounding of the expanded arterial walls. When arterial stiffness increases, the cushioning function is impaired, leading to a higher systolic and lower diastolic blood pressure. (Fig. 2)

Arterial stiffness is determined by structural and functional components related to the intrinsic elastic properties of the artery. Elastic properties are the qualities that enable the artery to stretch while retaining its ability to return to its original shape when excess stress (i.e. the pressure) is removed. The endothelium, the elastic tissue within the intimal medial layer, and smooth muscle contribute to arterial stiffness. Elastic fibers, elastin and collagen, are located within the intimal medial layers; at low and normal pressures, the elastin fibers mediate stiffness, while at higher pressures (systolic blood pressure greater than 200 mmHg), collagen fibers do. Differences in the ratio of elastin to collagen affect arterial stiffness. The lower the ratio of elastin to collagen, the stiffer the artery. Elevated smooth muscle tone or smooth muscle cell hypertrophy also increase arterial stiffness.

MEASUREMENT OF ARTERIAL STIFFNESS

Measures of arterial stiffness estimate the artery's ability to expand and contract with cardiac pulsation and relaxation. Technologic advancements have provided for direct, noninvasive visualization of arteries with excellent precision, opening the horizon for studies of arterial stiffness in research and clinical practice. While there is currently no gold standard, several measures have been used extensively in a variety of settings.

Pulse Pressure

The difference between systolic and diastolic blood pressure is often used to measure arterial stiffness. Pulse pressure reflects the pulsatile component of blood pressure. It reflects two major components: the interaction of ventricular ejection with the viscoelastic properties of the large arteries,
and the amplitude and duration of the pressure pulse-wave reflection from smaller arteries downstream. Although considered a crude estimate of arterial stiffness, a number of recent publications indicate that pulse pressure is a powerful predictor of cardiovascular events. (Fig. 3)

**Pulse Wave Velocity**

Pulse wave velocity measures arterial stiffness indirectly since it is influenced by a number of factors, including wall thickness, vessel radius, or blood density independent of arterial stiffness. The velocity of travel of a pressure wave along an artery is related to the stiffness of an arterial segment between measurement sites. Pressure waveforms are captured by a strain-gauge or transducers placed over the artery; velocity is estimated by dividing the distance traveled between transducers (meters) by the time of the travel of the pulse wave. (Fig. 4)

Increased smooth muscle tone or vascular hypertrophy, blood pressure, velocity of blood flow, or blood density may accelerate PWV. Apart from these anatomic and physiologic influences, measurement site contributes to PWV: the greater the distance from the heart the higher the PWV. A commercially available instrument to measure PWV is the Complior.

**Ultrasound and Doppler Techniques**

Ultrasound techniques allow visualization of wall thickness and vessel diameter. The ultrasound transducer is placed to direct ultrasound beams perpendicular to the artery to obtain the optimal sound reflection from the wall; two dimensional views of the reflected echoes from the wall and lumen are
displayed on a video monitor. Blood pressures concurrently measured, usually in the brachial artery, are used to adjust the change in diameter to estimate arterial stiffness. One of the most common (and the closest conceptually to stiffness) is the stress-strain elastic modulus (Ep), the ratio of stress (the difference in the systolic and diastolic blood pressure, i.e. pulse pressure) to strain (the percent change in the arterial diameter during the cardiac cycle, i.e. diameter change divided by diastolic diameter). Other measures include arterial compliance, where cross-sectional volume change is divided by pulse pressure. The stiffness index, similar conceptually to Ep, is the logarithm of the ratio of systolic to diastolic blood pressure divided by strain; it was developed to reduce the impact of pressure on the measurement of stiffness.

Augmentation Index

Large conduit arteries, such as the aorta, serve as capacitors and as cushions, smoothing cardiac pulsation, absorbing the oscillations generated from reflected waves, and directing blood through the organs and tissues in a steady stream. These oscillations can be observed in a pressure waveform. The augmentation index attempts to measure the height of a reflected wave relative to the incident wave to quantify the stiffness of the artery. A low compliance results in high augmentation index (AI). An instrument to measure AI is also commercially available (CardioVision). Mathematically modelling is used to infer arterial stiffness from the pressure waveform. (Fig. 5)

![Augmentation Index](image)

Figure 5

Pulse Contour Analysis

Pulse contour analysis (PCA) provides measurements that capture both capacitive (storage) and cushioning (oscillatory) arterial functions. It uses the arterial pulse contour to provide an assessment of the large artery (capacitance) behavior and the behavior of smaller arteries that represent the primary source of reflected waves or oscillations in the arterial system. The pulse waveform is analyzed using a modified Windkessel model. The model includes two compliance elements (generally referred to as $C_1$ and $C_2$) combined with inertance and resistance elements. The decay in the diastolic pressure waveform is determined by an algorithm that consists of the sum of an exponential decay and an exponentially-decaying sinusoidal term. The first term accounts for the overall fall of pressure during diastole, and the second term represents the oscillatory decay of the diastolic wave "superimposed" on the primary decay pattern. This system is also commercially available (HDI). Compliance is determined as a function of both the arterial system’s capacitance ($C_1$) and reflectance or oscillation ($C_2$). The former ($C_1$) reflects large artery compliance while the latter ($C_2$) reflects the small vessel compliance. (Fig. 6)
ARTERIAL STIFFNESS IS ASSOCIATED WITH HYPERTENSION IN DIFFERENT POPULATIONS

As arterial pressure rises, arterial compliance decreases. Debated is whether reductions in arterial compliance are transient (i.e., arteries return to normal levels as blood pressure normalizes) or irreversible. There is considerable evidence to suggest that sustained elevations in blood pressure accelerate atherosclerosis, arterial smooth muscle hyperplasia and hypertrophy, and collagen synthesis, thereby decreasing arterial compliance (perhaps irreversibly). We have been involved in two studies that support the role that arterial stiffening precedes the development of hypertension.

The Minnesota Children's Blood Pressure Study

This study was started in the 1977-78 school year with the blood pressure screening of 10,423 first through third grade children in the Minneapolis Public Schools. Following this screening, about 1,200 children were selected for long term evaluation because their blood pressure fell in the upper or lower fifth percentiles of the race-specific blood pressure distribution. An examination of 817 participants was conducted within two years of post high school. About five years after the post high school visit, 679 underwent reexamination between 1993 and 1995 (age 23.6±0.1 years), and a sample of 179 subjects was selected for measurement of pulse contour analysis (PCA). In PCA, the first measure represents large artery compliance ($C_1$), estimated as the exponential decay of the waveform. The second ($C_2$) represents the small artery compliance which determine peripheral wave reflections, measured as the diastolic fluctuation in the waveform that occur when wave reflections are superimposed on the basic shape of the waveform.

We divided $C_1$ (large artery compliance) and $C_2$ (small artery compliance) into quartiles and evaluated the relation of systolic blood pressure to systolic blood pressure using analysis of covariance models adjusted for sex, height, weight, insulin, and HDL and LDL cholesterol,. The mean of $C_1$ was $2.13 \pm 0.59$ ml/mmHg (range 0.80 to 4.36 ml/mmHg) and the mean of $C_2$ was $0.083 \pm 0.02$ ml/mmHg (range 0.04 to 0.14 ml/mmHg). Adjusted $C_1$ fell sharply and consistently across the systolic blood pressure ($p<.001$), indicating a strong inverse relationship between blood pressure and large artery compliance in young adults without hypertension. (Fig. 7)
The relationship between adjusted $C_2$ and systolic blood pressure was not as consistent, although it was statistically significant ($p=0.02$). $C_2$ was highest in the lowest systolic blood pressure quartile compared to the other three. (Fig. 8)
These results lend support to the hypothesis that abnormalities in arterial compliance contribute to the development of essential hypertension. Participants were measured at 23.6 years of age. While the large arteries may have undergone subtle atherosclerotic changes, the natural history of atherosclerosis suggests the absence of significant structural changes in the arteries of these young adults. Participants were not hypertensive, and the mean blood pressure was in the optimal blood pressure range (124.9/66.7 mmHg). Therefore, this inverse relationship between blood pressure and arterial compliance was detected prior to the onset of clinically apparent essential hypertension.

The Atherosclerosis Risk in Communities (ARIC) Study

This study, initiated in 1986, included about 16,000 participants from Forsyth County, North Carolina, selected suburbs of Minneapolis, Minnesota, Jackson, Mississippi, and Washington County, Maryland. A cohort of about 4,000 adults between the ages of 45 and 64 years was drawn from a probability sample from each participating community. All hypertensives at baseline were excluded from the analysis, and the incidence of hypertension, defined as a systolic blood pressure greater than 160 mmHg or diastolic blood pressure > 95 mmHg or taking antihypertensive medication. Arterial stiffness was measured using ultrasound (Biosound 2000II) in conjunction with an electronic tracking device that tracked linearly amplified radio frequency echoes arising from the carotid arterial wall, detected at the center of the ultrasound image. Concurrent brachial artery blood pressure measurements were taken with an oscillatory blood pressure monitor.

The arterial stiffness indices for a given individual are defined as the ratio of the change in intraluminal pressure to change in the arterial diameter over the cardiac cycle. We adjusted the change in arterial diameter by Age, race, height, HDL and LDL cholesterol, common carotid artery intima-media thickness and diastolic arterial diameter were also included as covariates. The adjusted diameter change is inversely related to stiffness (the smaller the change in diameter, the stiffer the artery). (Fig. 9)

![Arterial stiffness and 6 year Incidence of Hypertension (BP > 160/95 or meds): Atherosclerosis Risk in Communities Study](image)

**ARTERIAL STIFFNESS MAY BE DETERMINED BY GENETIC FACTORS**

While little is known about the genetics of arterial compliance, there is some evidence to suggest that arterial compliance is determined, in part, by genes. A standard approach to the assessment of genetic etiology is to examine the trait is heritable. Heritability can be thought of as the correlation of the trait
within family members: a high degree of correlation suggests a genetic component to the trait. Heritability is crudely defined as twice the level of the sibling correlation. We evaluated the heritability of pulse pressure, a surrogate marker of arterial stiffness, in the NHLBI Family Heart Study (FHS). FHS is a multicenter, family-based study of genetic and nongenetic determinants of coronary heart disease. Within this cohort of families, about 6,000 adults ages 18 - 95 years, we found the heritability of pulse pressure to be 34%.

To examine whether there were regions on the human genome that harbored genes contributing to arterial stiffness, we examined a subset (1161 total individuals) based on family size (i.e., larger families). We used genetic markers, typed by the NHLBI Mammalian Genotyping Service, to test for linkage of regions of the genome to pulse pressure using a variance components linkage method. Pulse pressure was adjusted for sex, age, height, field center, triglycerides, creatinine clearance and fibrinogen. Statistical significance was defined by the lodscore, which in this particular program was the likelihood ratio of estimated quantitative trait locus (QTL) variance compared to the QTL variance equal to zero (i.e., no genetic linkage). The standard criterion for significance is a lodscore > 3.0. (Fig. 10)

Based on this linkage analysis, there appears to be a gene contributing to pulse pressure on chromosome 8, that is located at 32 cM. This region also contains the lipoprotein lipase (LPL) gene which has been associated with hypertension. LPL may be an important candidate gene for pulse pressure.

We further evaluated the role of genetic factors in arterial stiffness in a second study, the Hypertension Genetic Epidemiology (HyperGEN) Network. HyperGEN recruited Caucasian and African American hypertensive sibships in four communities (Birmingham, AL; Forsyth County, NC; Minneapolis, MN; and Salt Lake City, UT). Eligible siblings met at least one of the following criteria: clinical diagnosis or treatment of hypertension before age 60, excluding hypertension diagnosed at pregnancy; current BP greater than or equal to 140/90 or current use of antihypertensive medications; or historical treatment of hypertension with prescribed medications for at least one year of the last five years. We measured arterial compliance using 2D guided M-mode echocardiograms (pulse pressure divided by the echocardiographic stroke volume). Genetic markers (n=387) were typed by the NHLBI Mammalian Genotyping Service. We conducted linkage analysis with multipoint variance components methods, and adjusted arterial compliance for age, field center and heart rate. The table describes the characteristics of the study population. (Table 1)
The sample is equally divided between African Americans and Whites, is moderately hypertensive and obese. When the linkage analysis was conducted, we detected suggested linkage of arterial compliance to a region on chromosome 2 (LOD =2.15, 231 cM from the pter) in African Americans. (Fig. 11)

These results suggest there may be influential genetic regions contributing to aortic compliance in African American sibships ascertained for hypertension. Collectively, these two studies, the first to our knowledge, indicate the presence of genetic factors influencing hypertension.

**SUMMARY**

It is apparent from our work that arterial stiffening is a precursor to hypertension, and that arterial stiffening is likely to have a genetic basis. It is also clear that early recognition of arterial changes may identify individuals at risk of clinical complications of hypertension, and may therefore provide for early modification of risk factors and delay or reverse the hypertensive process.
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