Arteries stiffen as a consequence of age and atherosclerosis. The two leading causes of death in the developed world, myocardial infarction and stroke, are both a direct consequence of atherosclerosis and increased arterial stiffness is associated with an increased risk of cardiovascular events. The World Health Organisation predicts that by 2010 cardiovascular disease will also be the leading killer in the developing world and represents a major global health problem.

Arterial stiffness

Once considered by the ancient Greeks as inert conduits within which air flowed, William Harvey is generally credited with being the first to describe the circulation of the blood through arteries. The circulation of blood depends on the contraction of the heart. When the heart contracts it generates a pulse or energy wave that travels through the circulation. The speed of travel of this pulse wave (pulse wave velocity) is related to the stiffness of the arteries. Other terms that are used to described the mechanical properties of arteries include elastance, or the reciprocal (inverse) of elastance, compliance. The relationship between arterial stiffness and pulse wave velocity (PWV) was first predicted by Thomas Young in his Croonian Lecture of 1808 (Young T: On the function of the heart and arteries: The Croonian lecture. Phil Trans Roy Soc 1809;99:l-31), but is generally described by the Moens-Korteweg equation (Nichols WW, O'Rourke MF. Vascular impedance. In: McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 4th ed. London, UK: Edward Arnold; 1998:54 97, 243 283, 347 395.) or the Bramwell-Hill equation (Bramwell JC, Hill AV. The velocity of the pulse wave in man. Proc R Soc Lond (Biol) 1922;93:298-306).Typical values of PWV in the aorta range from approximately 5m/s to >15m/s.

Measurement of aortic PWV provides some of the strongest evidence concerning the prognostic significance of large artery stiffening. Increased aortic PWV has been shown to predict cardiovascular and in some cases all cause mortality in individuals with end stage renal failure (Blacher et al.,Circulation. 1999; 99: 2434 2439), hypertension (Laurent et al., Hypertension. 2001; 37: 1236 1241), diabetes mellitus (Cruickshank et al., Circulation. 2002; 106: 2085 2090) and in the general population (Mattace-Raso et al. Circulation. 2006;113:657-663, Hansen et al., Circulation. 2006;113:664-670.). However, at present, the role of measurement of PWV as a general clinical tool remains to be established.

Is Arterial Structure Important?

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Increasingly, in recent years, the stiffness of large elastic arteries has been recognized as a major determinant of vascular function and cardiovascular risk.[1,2] The distally propagating arterial pressure pulse is reflected at arterial branch points (sites of impedance mismatch), and the velocity and magnitude of these reflections is determined by arterial stiffness. Whereas peripheral vascular resistance largely determines diastolic BP, central systolic BP and pulse pressure are influenced by the augmentation of aortic pressure because of wave reflections, as well as by the character of ventricular ejection. Increased stiffness leads to greater pulsatile stress and strain and may influence endothelial shear stress, contributing to remodeling and structural abnormalities of the blood vessel wall and to atherogenesis. An increase in aortic stiffness also results in an increase in left ventricular afterload and, consequently, myocardial oxygen consumption[3] and compromise of myocardial perfusion during diastole, particularly in the subendocardial region.[4] That central arterial stiffness is clinically relevant is evident from the studies showing a positive predictive value of aortic stiffness for cardiovascular risk in hypertension,[5,6] although the precise mechanism of this association remains unclear.

Arterial stiffness is largely determined by 2 influences: first, those related to the arteries themselves (wall structure and function and lumen size); and, second, the mean distending arterial BP. The main load-bearing components of the arterial wall are elastin fibers, stiffer collagen fibers, and vascular smooth muscle. Smooth muscle contraction results in increased arterial stiffness because of a decrease in lumen size and shifting of load onto stiffer collagen fibers. Increasing mean distending pressure causes a small increase in lumen size. However, transfer of stress from elastin to collagen fibers outweighs this effect, leading to an exponential increase in arterial stiffness with pressure. Given that arterial stiffness is increased in patients with essential hypertension and that arterial remodeling is a recognized feature of hypertension,[7] an important question has been whether increased aortic stiffness is fully accounted for by the increase in mean distending pressure or whether there are intrinsic wall changes secondary to structural or functional effects. Indeed, this may be of importance in selecting treatment for individual patients.

To examine what effects the inherent properties of the vessel wall have on arterial stiffness, measures such as compliance, distensibility, pulse wave velocity (PWV), or elastic modulus must be compared under isobaric conditions. Previous work has either used pressure-compliance curves with interpolation of stiffness at a given blood pressure (BP)[8] or has normalized transmural pressure by placing the arm in a pressurized air chamber.[9] However, in this issue of *Hypertension*, Stewart et al[10] describe a method for generating isobaric conditions using a pharmacological intervention that acutely normalized the loading pressure in hypertensive subjects, dispensing with some of the assumptions associated with other methods. Stewart et al[10] studied 20 subjects with treated but inadequately controlled essential hypertension and 20 matched normotensive controls. Acutely reducing mean arterial pressure in the normotensive subjects, using glyceryl trinitrate (GTN), caused a corresponding reduction in arterial stiffness, as quantified by carotid-femoral PWV (PWV_{CF}) and carotid distensibility. However, when mean pressure in the hypertensive patients was reduced to the baseline level of the normotensive individuals, there was no change in either PWV_{CF} or arterial distensibility. Furthermore, using angiotensin II to increase the mean arterial pressure of normotensive subjects to the baseline level of the hypertensive individuals, arterial stiffness increased but still remained lower in the normotensive subjects. These findings suggest that the increase in aortic stiffness seen in

hypertensive patients is because of an increase in intrinsic wall stiffness rather than simply elevated BP and may also imply a degree of resistance to changes of distending pressure. Importantly, this is in contrast to results from experiments using alternative techniques, which suggest that the increase in arterial stiffness in hypertensive individuals is largely because of the increase in mean pressure.[8,9] The 2 questions one must surely ask are, first, why do these findings seem to disagree with the findings of others using different methodology, and second, what relevance might these observations have from a clinical perspective?

Estimation of isobaric compliance from pressure-diameter curves[8] requires important assumptions to be made, and it can be argued that the full pressure–diameter relationship should be considered rather than 1 value in the cardiac cycle. Because the vessel wall is viscoelastic, luminal diameter at a given pressure is affected by the nature of the preceding pressure curve. This results in the compliance–pressure relationship exhibiting hysteresis, which must either be "removed" or ignored to create a curve from which compliance can be calculated at any given BP. This curve-fitting procedure may result in a potentially large error in the estimate of compliance and, additionally, mask differences between 2 clearly distinct pressure–compliance loops. Furthermore, this approach disregards potential differences in the pressure–compliance loop that might exist at truly different distending mean pressures. Normalizing transmural pressure using mechanical means[9] removes the potential inaccuracy introduced by such mathematical assumptions. However, it ignores systemic hemodynamic differences, such as wave reflections, that may exist. It can also only be used to examine conduit vessels and not large central arteries. The administration of a pharmacological agent (in this case GTN) is, of course, not without problems either. Small doses of GTN do not seem to change BP or PWV_{CF}. It is possible, however, that the larger doses of GTN used in this study altered the intrinsic aortic wall stiffness independent of the reduction in mean BP. Furthermore, the aortic wall response to GTN may have differed between the hypertensive and normotensive groups. Alternatively, the duration of GTN administration may have been of sufficient duration to induce reflex neurohormonal responses to the hypotension induced and act in a counterregulatory way to maintain a higher PWV_{CF} in the hypertensive patients: pressure-diameter relationships are captured within the pressure excursions of a single cardiac cycle and have the potential advantage that they are not subject to such unknown hemodynamic changes. This was a relatively small study, and the findings would benefit from confirmation, including studies in previously untreated patients. In addition, there is a lack of data describing the changes in arterial stiffness in response to acute BP lowering with drugs other than GTN, and this is an important area for future work. Nonetheless, use of pharmacological intervention to achieve isobaric conditions would seem more clinically applicable than previous methodology, given that PWV_{CF} can adversely affect central BP and cardiac function and is closely linked to cardiovascular risk.

Why are these findings potentially clinically relevant? Arterial stiffness is a risk factor for cardiovascular disease, independent of BP, and the study from Stewart et al[10] suggests that simply lowering BP may not necessarily be sufficient to address this important risk factor. Indeed, other work[2] has shown that antihypertensive treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and calcium-channel blockers reduces arterial stiffness, whereas thiazide diuretics have less favorable effects, and ß-blockers have little impact. The study by Stewart et al[10] suggests that hypertensive remodeling is likely to be important, so any beneficial response is likely to take time to occur, either through direct effects

on the arterial wall or because of reduced shear stress or pulsatile load. This would fit with recent work[11] showing that larger doses of perindopril increase distensibility while having no additional effect on BP, consistent with a direct effect on intrinsic wall stiffness. Some newer agents targeting endothelial dysfunction or those directly affecting arterial structure, such as advanced glycation end-product crosslink breakers,[12] may also offer promise in this area. Nevertheless, the failure of arterial stiffness to improve with thiazides, drugs with established morbidity and mortality advantages in hypertension, serves as a reminder that BP reduction per se remains of prime importance. More work is clearly indicated, using the powerful tools now available, to establish the mechanisms whereby chronic lowering of BP, using established and newer agents, reduces arterial stiffness and improves clinical outcome.

Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients.

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Although various studies reported that pulse pressure, an indirect index of arterial stiffening, was an independent risk factor for mortality, a direct relationship between arterial stiffness and all-cause and cardiovascular mortality remained to be established in patients with essential hypertension. A cohort of 1980 essential hypertensive patients who attended the outpatient hypertension clinic of Broussais Hospital between 1980 and 1996 and who had a measurement of arterial stiffness was studied. At entry, aortic stiffness was assessed from the measurement of carotid-femoral pulse-wave velocity (PWV). A logistic regression model was used to estimate the relative risk of all-cause and cardiovascular deaths. Selection of classic risk factors for adjustment of PWV was based on their influence on mortality in this cohort in univariate analysis. Mean age at entry was 50+/-13 years (mean+/-SD). During an average follow-up of 112+/-53 months, 107 fatal events occurred. Among them, 46 were of cardiovascular origin. PWV was significantly associated with all-cause and cardiovascular mortality in a univariate model of logistic regression analysis (odds ratio for 5 m/s PWV was 2.14 [95% confidence interval, 1.71 to 2.67, P<0.0001] and 2.35 [95% confidence interval, 1.76 to 3.14, P<0.0001], respectively). In multivariate models of logistic regression analysis, PWV was significantly associated with all-cause and cardiovascular mortality, independent of previous cardiovascular diseases, age, and diabetes. By contrast, pulse pressure was not significantly and independently associated to mortality. This study provides the first direct evidence that aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in patients with essential hypertension.

Aortic Stiffness Is an Independent Predictor of Primary Coronary Events in Hypertensive Patients

A Longitudinal Study

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Arterial stiffness may predict coronary heart disease beyond classic risk factors. In a longitudinal study, we assessed the predictive value of arterial stiffness on coronary heart disease in patients with essential hypertension and without known clinical cardiovascular disease. Aortic stiffness was determined from carotid-femoral pulse wave velocity at baseline in 1045 hypertensives. The risk assessment of coronary heart disease was made by calculating the Framingham risk score according to the categories of gender, age, blood pressure, cholesterol, diabetes, and smoking. Mean age at entry was 51 years, and mean follow-up was 5.7 years. Coronary events (fatal and nonfatal myocardial infarction, coronary revascularization, and angina pectoris) and all cardiovascular events served as outcome variables in Cox proportional-hazard regression models. Fifty-three coronary events and 97 total cardiovascular events occurred. In univariate analysis, the relative risk of follow-up coronary event or any cardiovascular event increased with increasing level of pulse wave velocity; for 1 SD, ie, 3.5 m/s, relatives risks were 1.42 (95% confidence interval [CI], 1.10 to 1.82; $P<0.01$) and 1.41 (95% CI, 1.17 to 1.70; $P<0.001$), respectively. Framingham score significantly predicted the occurrence of coronary and all cardiovascular events in this population ($P<0.01$ and $P<0.0001$, respectively). In multivariate analysis, pulse wave velocity remained significantly associated with the occurrence of coronary event after adjustment either of Framingham score (for 3.5 m/s: relative risk, 1.34; 95% CI, 1.01 to 1.79; $P=0.039$) or classic risk factors (for 3.5 m/s: relative risk, 1.39; 95% CI, 1.08 to 1.79; $P=0.01$). Parallel results were observed for all cardiovascular events. This study provides the first direct evidence in a longitudinal study that aortic stiffness is an independent predictor of primary coronary events in patients with essential hypertension

Folic Acid and Arterial Stiffness

The search to understand the underlying mechanism for cardiovascular disease is always underway. In the last 2 decades enormous advancements have been made in the understanding of cardiovascular disease risk. In the last 10 years the medical community has established several independent markers of cardiovascular disease risk, including homocysteine.

Homocysteine is a by-product of the production of DNA. It is usually created from one biochemical reaction and then another reaction removes it from our system. Homocysteine can

build up in the system if folic acid or Vitamin B12 is deficient. Higher levels of homocysteine in the blood increase the risk for cardiovascular disease.

Folic acid is one vitamin cofactor that has been proven in clinical trials to decrease the levels of homocysteine in the blood. Folic acid is a cofactor in the reaction that reduces homocysteine into methionine. Because of the action that folic acid has on homocysteine, it reduces cardiovascular disease risk.

Aside from the effect on homocysteine, folic acid may have other means of decreasing cardiovascular disease. A study published in the American Journal of Clinical Nutrition examined the possibility that folic acid supplementation reduces arterial stiffness, therefore reducing risk of cardiovascular disease.

The study enrolled 41 men with normal to high normal blood pressure. The participants were given 5mg of folic acid for 3 weeks. The outcome measures were blood pressure in the brachial pulse (taken in arm) and mean arterial pressure (MAP). Arterial compliance was also assessed as well as serum concentrations of folate and homocysteine.

The results showed that supplementation of 5mg of folic acid alone-reduced blood pressure by 5mmHg. There was no effect observed on MAP. Supplementation also increased systemic arterial compliance, meaning the arteries had increased elasticity in response to changes in blood pressure. There were no correlations between the increased compliance and serum levels of folate and homocysteine

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.

www.**healthandage.com**/html/res/aging_of_you/content/11.html

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