

## Changes in Blood Pressure and Vascular Physiology: Markers for Cardiovascular Disease

Based on a presentation by Joseph L. Izzo, Jr., MD

### **Presentation Summary**

Changes in systolic and diastolic blood pressure are markers of altered vascular physiology and premature cardiovascular disease. Perhaps the most important markers to note are systolic pressure and pulse pressure, both of which are superior to diastolic pressure in predicting cardiovascular morbidity and mortality. They are also surrogates for arteriosclerosis or "hardening of the arteries."

Arteriosclerosis, which involves excess collagen deposition, is different from atherosclerosis, which involves an inflammatory response to lipid oxidation. Arteriosclerosis plays a major role in the genesis of systolic hypertension and in the sequelae of hypertension. Thus, there is a clinical need for measuring arterial stiffness. It is probable that stiffness of the large vessels is linked to a number of other adverse changes in the distal circula-

tion. Indeed, the degree of arteriosclerosis, which increases with age, leads directly to left ventricular hypertrophy (LVH) because of the phenomenon of wave reflection and central pulse augmentation.

Evidence suggests that arteriosclerosis and LVH not only occur in parallel but can be reversed in parallel.

Several different methods are being used or developed to measure arterial compliance in clinical practice. These include cuff measurements of systolic blood pressure and pulse pressure, pulse pressure/stroke volume, pulse wave velocity, pulse contour analysis (using either Windkessel computations of proximal and distal compliance or reflectance computations of central augmentation pressure, augmentation index, and the central time-tension index), Doppler ultrasound, and limb plethysmography.

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**A** great deal of evidence indicates that different patterns of change in blood pressure are markers for cardiovascular disease, said Joseph L. Izzo, Jr., MD, Professor of Medicine and Pharmacology, Chief,

Director of Clinical Pharmacology, State University of New York at Buffalo.

From this evidence—including population studies, clinical trials, and research in hypertension and

vascular physiology— one can draw several major conclusions (Table 1), Dr. Izzo noted. Perhaps the most important conclusion is that systolic pressure and pulse pressure are superior to diastolic pressure in predicting cardiovascular morbidity and mortality, most probably because they are surrogates for arteriosclerosis.

To illustrate these points, Dr. Izzo reviewed data from epidemiologic and clinical trials, the relationship between systolic hypertension and large vessel stiffening, the difference between arteriosclerosis and atherogenesis, reflected wave theory, the impact of systolic hypertension on target organ damage and control mechanisms, the role of angiotensin-converting enzyme (ACE) inhibition in treating vascular and cardiac hypertrophy, and several techniques to measure arterial compliance.

### Epidemiologic and Clinical Trial Data

One study that evaluated the impact of wide pulse pressure on cardiovascular morbidity and mortality involved more than 2200 patients with controlled hypertension who were followed for 20 years.<sup>1</sup> When the investigators divided the patients into 3 groups on the basis of pulse pressure, they found a statistically significant increase in the incidence of myocardial infarction (MI) and all-cause cardiovascular deaths in those with the widest pulse pressures (Table 2),<sup>2</sup> Dr. Izzo pointed out.

Because the mean pressures and systolic pressures were higher in tertile 3 but the diastolic pressures only a bit lower than those in Tertiles 1 and 2, the investigators looked at the incidence of MI in the same patients on the basis of pulse pressure tertile and the degree of reduction in diastolic blood pressure (Table 3). They found the incidence of MI increased as diastolic pressure decreased.<sup>2</sup> Thus, after classification of hypertension jointly by systolic and diastolic

blood pressure, an increase in diastolic pressure confers a better risk profile.

The significance of pulse pressure was further demonstrated in a reanalysis of the Framingham Study data by 2 teams of investigators, he continued. Franklin et al found a strong relationship between age and both systolic pressure and pulse pressure.<sup>3</sup> More recently the other team found, after classification of hypertension jointly by systolic and diastolic blood pressure, morbidity and mortality were correlated positively with systolic pressure and inversely with diastolic pressure. The team also found that pulse pressure correlations with morbidity and mortality were marginally stronger than systolic pres-

**Table 1.** Conclusions Regarding Changes in Blood Pressure and Vascular Physiology as Markers for Cardiovascular Disease

<ul style="list-style-type: none"> <li>■ Systolic and pulse pressures are superior to diastolic pressure in predicting cardiovascular morbidity and mortality.</li> <li>■ Therapeutic trials, especially the Systolic Hypertension in the Elderly Program (SHEP), clearly demonstrate that treatment of isolated systolic hypertension reduces mortality and the rates of heart attack, heart failure, stroke, and kidney failure.</li> <li>■ Systolic hypertension and wide (peripheral) pulse pressure are most commonly related to arteriosclerosis and decreased vascular compliance, especially in the elderly.</li> <li>■ Decreased vascular compliance and increased systemic resistance are major factors in cardiac hypertrophy.</li> <li>■ Microcirculatory pathology, including capillary rarefaction, metabolic abnormalities, and organ dysfunction, may be linked to macrovascular pathology.</li> <li>■ The sympathetic nervous system and angiotensin II accelerate pressure-induced hypertrophy of vascular and cardiac tissue, and ACE inhibition can increase large artery compliance in man.</li> <li>■ Arterial compliance(s) can be measured noninvasively by several techniques, each of which provides unique information about vascular biomechanics.</li> </ul>
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sure alone (Personal Communication, Daniel Levy, MD, 1999).

“These findings are striking,” Dr. Izzo said. “The inverse relationship of risk with diastolic pressure means

that the higher the diastolic pressure, the better a patient will do. This contrasts strongly with the positive correlations of risk with systolic and pulse pressures.”

Noting that many studies have shown that treating systolic hypertension has a greater gain on morbidity and mortality than is immediately obvious, Dr. Izzo turned his attention to the SHEP trial. In that study, active treatment with chlorthalidone effectively lowered systolic blood pressure, with reductions of 12 to 14 mm Hg systolic (from about 170 mm Hg), and also lowered diastolic pressure by 2 to 4 mm Hg (from about 75 mm Hg) over 5 years.<sup>4</sup> The principal endpoint was stroke reduction, and those on active treatment had a far lower cumulative rate of fatal plus nonfatal stroke over the 5-year study period than did those receiving placebo.

In addition, the reduction in relative risk for stroke and other potential endpoints—transient ischemic attacks, left ventricular failure, MI, and subsequent coronary artery bypass grafting or angioplasty—was truly impressive in those on active treatment compared with those receiving placebo. This was particularly true for heart failure.<sup>4</sup>

“The reduction in relative risk for myocardial infarction was statistically significant and greater than the benefit predicted in trials focusing on diastolic blood pressure. This suggests to me that systolic blood pressure is closer to the action and tells us more of what we want to know about practical therapeutics,” Dr. Izzo remarked.

### Hemodynamics of Arteriosclerosis

Arteriosclerosis is different from atherosclerosis, which is different from atherosclerosis, he continued.

Arteriosclerosis is an age-related change in structure and function of the muscularis layer of large arteries. It is characterized by increasing artery wall stiffness as elastin is replaced by collagen. Arterial diame-

**Table 2.** Impact of Wide Pulse Pressure on Cause-Specific Morbidity and Mortality

Event	Incidence per 100 Person-Years by Pulse Pressure Tertile		
	Tertile 1 ≤ 46 mm Hg	Tertile 2 47-62 mm Hg	Tertile 3 ≥63 mm Hg
Myocardial infarction	3.5	2.9	7.5
Stroke	1.2	2.3	2.9
Cardiovascular disease	5.2	6.6	13.6
Cardiovascular disease	1.7	4.3	7.5

There were 735 patients in tertile 1, 726 in tertile 2, and 746 in tertile 3. Source: Reference 2.

**Table 3.** Incidence of Myocardial Infarction per 1000 Person-Years by Tertile of Blood Pressure and Degree of Reduction in Diastolic Blood Pressure

Pulse Pressure Tertile	Fall in Diastolic Blood Pressure		
	Large ≥ 18 mm Hg	Medium 7-17 mm Hg	Small ≤6 mm Hg
Tertile 1 (≤ 46 mm Hg)	3.2	2.8	5.5
Tertile 2 (47-62 mm Hg)	3.4	2.6	2.3
Tertile 3 (≥ 63 mm Hg)	9.5	3.9	11.2
Total	5.9	3.1	6.9

Large falls in diastolic blood pressure were seen in 604 patients, medium falls in 1102, and small falls in 501. Source: Reference 2.

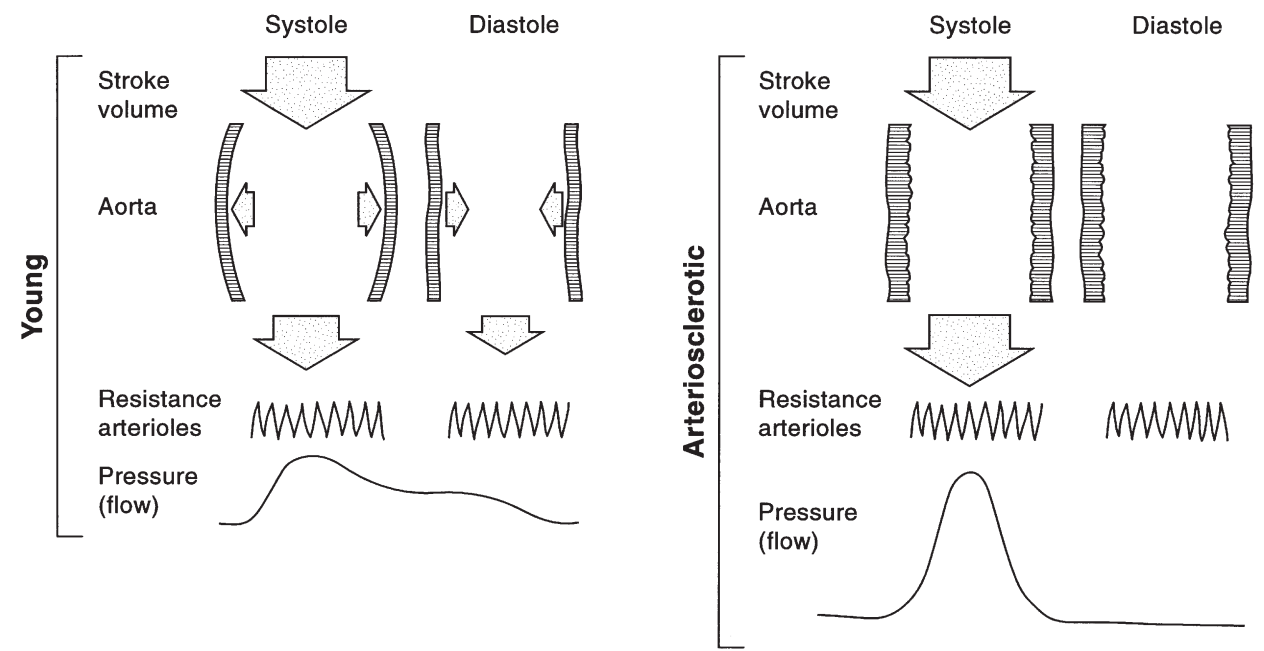
ter and wall tension, pulse wave velocity, and systolic and pulse pressures increase. Arteriosclerosis can also occur as a late stage of atherosclerosis, which results from the coexistence of arteriosclerosis and atherosclerosis, which is an occlusive inflammatory process that involves endothelial dysfunction and increased oxidative metabolism of excess low-density lipoproteins.

Dr. Izzo then reviewed normal aortic pulsatile function in adults and the pathogenesis of isolated systolic hypertension and widened pulse pressure in the elderly. In the normal young aorta, a fraction of each cardiac stroke volume distends

the elastic large arteries and is retained there during systole. Elastic recoil of the compliant large arteries acts as a secondary pump, emptying the incremental systolic arterial volume into the distal circulation during diastole. The result is that a degree of forward flow continues during diastole and the pulse pressure remains relatively narrow (Figure, left panel).

In contrast, the stiffened arteriosclerotic aorta loses its elastic recoil and reservoir function, causing a greater proportion of each cardiac stroke volume to be delivered to the peripheral circulation during systole.

**Figure.** Hemodynamics of Arteriosclerosis: Effect of Decreased Large Vessel Distensibility



When a stroke volume is applied during systole to the distensible aorta in the panel on the left, a fraction of it is retained (as shown by the smaller arrows) while the greater proportion comes through the resistance arterioles. During diastole, this incremental stroke volume is delivered to the peripheral circulation by the elastic aorta. The relatively smooth pulse contour corresponds to a narrow pulse pressure (eg, 140/110 mm Hg). In the stiff, lead-pipe aorta shown in the panel on the right, the entire stroke volume is delivered through the resistance arterioles during systole. The relatively steep pulse contour corresponds to an increased systolic and decreased diastolic blood pressure (220/70 mm Hg). Each has the same mean arterial pressure and increased vascular resistance.

The pulse pressure widens (systolic pressure increases and diastolic pressure decreases) because of the proportional increase in flow during systole and decrease in flow during diastole (Figure, right panel).

These 2 extremes represent the impact on the distal circulation, Dr. Izzo said, adding that there is also the central point of view to consider because pulse waves reflect backward to the heart from the distal circulation at various points.

Specifically, arterial pulse waves are compression waves that travel downstream (antegrade) at a greater velocity than the blood itself. Reflection, or augmentation, occurs at points of mismatched impedance, including points of sudden change in wall stiffness, bifurcations, areas of turbulence or flow velocity change, and constricted areas.

In stiffer vessels with increased pulse wave velocity, reflected waves return to the aortic root in late systole, augmenting and prolonging peak systolic pressure. This pulse wave augmentation markedly increases the mechanical load on the left ventricle and is a major contributing factor to left ventricular hypertrophy (LVH) and further aortic arteriosclerosis.

### **Clinical and Cardiac Effects**

The arteriosclerotic process, which increases with age, is critical to understanding who is at risk for developing LVH and to understanding the parallels between vascular stiffness and cardiac hypertrophy, which are governed by many of the same influences at the same time, Dr. Izzo observed.

Looking at the cardiac effects of increased systolic and diastolic pressures within this construct, it is apparent that increases in systolic pressure are responsible for direct increases in impedance and heart wall tension, direct promotion of LVH and, later on, progression to ventricular overload and failure. Because they

are closely related to increased oxygen consumption, increases in systolic blood pressure worsen angina and precipitate MI.

Increased diastolic pressure is different, he noted. Diastolic blood pressure has an indirect effect on impedance via increased aortic distention and increased wall tension resulting from increased lumen diameter. Increased diastolic blood pressure is also associated with improved coronary filling, especially in patients with coronary artery disease, and with lesser increases in oxygen consumption and angina than systolic blood pressure.

Because arteriosclerosis impairs arterial pressure sensors (ie, aortocarotid baroreflexes), it also leads to a number of dysregulatory consequences. These include diminished blood pressure buffering and increased systolic pressure variability, increased sympathetic nervous output, increased supine blood pressure, and impaired postural adaptation, sometimes with postural hypotension. Indeed, a number of small studies have shown that people with the greatest degree of arteriosclerosis are the ones who are at greatest risk for sudden death and untoward complications of hypertension, Dr. Izzo pointed out.

Moreover, it is probable that increased stiffness of the large vessels is linked to microcirculatory changes such as capillary dropout or rarefaction, which is associated with metabolic disturbances (including insulin resistance), abnormal capillary flow heterogeneity, increased capillary pulsation, increased microcirculatory damage, and possibly an increased rate of parenchymal atrophy in the brain, kidney, and eye.

### **Reversing Arteriosclerosis**

Evidence indicates that arteriosclerosis can be reversed, that stiff vessels can be softened, at least to a degree. A study evaluating lisinopril

versus metoprolol demonstrated that, after 10 weeks of therapy, lisinopril increased the distensibility of the carotid artery, whereas metoprolol decreased the distensibility slightly.<sup>5</sup>

In addition to lowering blood pressure, it appears that ACE inhibitors have direct effects on vascular stiffness. It is also possible that combined functional and structural changes may be related to overreactivity of the renin-angiotensin system and that angiotensin antagonists may be the drugs of choice in reversing arteriosclerosis, Dr. Izzo noted.

If vascular stiffness can be reversed, it should be possible to reverse cardiac hypertrophy more effectively as well, he continued. Although this is a topic of some controversy, a meta-analysis by Dalhof has shown that ACE inhibitors are more effective than diuretics,  $\beta$ -blockers, and calcium channel blockers in reducing left ventricular mass for roughly equal reductions in blood pressure.<sup>6</sup>

### Measuring Arterial Compliance

Various methods are being used or developed for measuring arterial compliance, beginning with simple cuff measurements of systolic blood pressure and pulse pressure, both of which have some relationship to events that are linked to arteriosclerosis. Other more specific methods include pulse pressure/stroke volume, pulse wave velocity (which is an indirect measure of vascular stiffness), pulse contour analysis, and Doppler ultrasound and limb plethysmography to estimate arterial wall characteristics, Dr. Izzo observed.

Pulse contour analysis may use either Windkessel computations (where C1 is the proximal or nonpulsatile compliance and C2 is the distal

or pulsatile—ie, oscillatory—compliance) or reflectance computations of central augmentation pressure, augmentation index, and the central time-tension index, which is the systolic area under the curve multiplied by time and may relate to LVH.

Doppler ultrasound can be used to estimate the internal diameter, wall stress, and wall strain/incremental elastic modulus of the carotid artery and arteries of the arm and leg. Limb plethysmography is intended for indirect estimation of the internal diameter and wall tension of arteries in the limbs.

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