Clinical Measurement of Arterial Stiffness Obtained From Noninvasive Pressure Waveforms

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Aortic pulse wave velocity (PWV) and augmentation index are independent predictors of adverse cardiovascular events, including mortality. In hypertension and aging, central elastic arteries become stiffer, diastolic pressure decreases, and central systolic and pulse pressures are augmented due to increased PWV and early return of reflected waves to the heart from the periphery. Valuable information on arterial properties such as stiffness can be obtained from both central (aortic) and peripheral (radial artery) pressure waveforms, but absolute values of wave reflection amplitude and wasted left ventricular (LV) pressure energy can only be obtained from the central arterial pressure waveform. As the arterial system becomes stiffer, there is a marked increase in central systolic and pulse pressures and wasted LV energy, along with a decrease in pulse pressure amplification. The increase in aortic systolic and pulse pressures are due primarily to increases in PWV and wave reflection amplitude with a small increase in incident wave amplitude. In individuals with very stiff elastic arteries (eg, in older persons with isolated systolic hypertension), there is a decrease in diastolic pressure. These changes in pressure components increase LV afterload and myocardial oxygen demand and therefore cause an undesirable mismatch between ventricle emptying and arterial pulse wave transmission, which promotes ventricular hypertrophy. High systolic and pulse pressures resulting from advanced age or hypertension increase circumferential arterial wall stress, which likely causes breakdown of medial elastin and increases the possibility of local fatigue, endothelial damage and development of atherosclerosis. Vasodilator drugs may have little direct effect on large central elastic arteries, but at the same time, their effects on peripheral muscular arteries reduce wave reflection amplitude and markedly lower systolic and pulse pressures and ventricular afterload. These beneficial effects on central arterial pressure can occur with or without a reduction in cuff blood pressure (BP) and may explain the apparent "pressure-independent" effects of drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Therefore, optimal treatment of high BP and its complications should include consideration of arterial stiffness, augmentation of aortic pressure, and LV wasted energy, all of which should be reduced to the lowest possible level. Am J Hypertens 2005;18:3S–10S © 2005 American Journal of Hypertension, Ltd.

> "However eloquent may be the words of a writer, he cannot in a page convey as clear an idea of the rhythm of the heart as a simple pulse-tracing, and if writers had given us more pulse-tracings, their works would have been greatly enhanced in value." (James Mackenzie, 1902)

The association between blood pressure (BP) and major cardiovascular events including stroke, myocardial infarction, organ damage, and mortality are well documented in both normotensive and hypertensive individuals, and this association is greatly influenced by age. Numerous observational epidemiologic studies and clinical trials, including the Framingham Heart Study, have shown a strong positive and continuous association between brachial artery sphygmomanometric systolic and pulse pressures and adverse cardiovascular events,[1–6] especially in individuals >50 years of age.[7] Furthermore, in a meta-analysis of seven randomized clinical trials, a J-shaped relationship between minimum diastolic BP and cardiovascular mortality was found.[8] Because systolic, diastolic, and pulse pressures are related to the physical properties of elastic arteries, attention has been directed toward arterial stiffness, pulse wave velocity (PWV), and wave reflections as cardiovascular risk factors.[9,10] Indeed, independent studies have shown that central arterial stiffness is increased in older individuals[11] and in those with coro-

Received September 30, 2004. Accepted October 4, 2004.

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0895-7061/05/$30.00
doi:10.1016/j.amjhyper.2004.10.009

nary artery disease,[12] myocardial infarction,[13] heart failure,[14] hypertension,[15,16] stroke,[17] diabetes mellitus,[18,19] end-stage renal disease,[20,21] hypercholesterolemia,[22] and inflammation.[23,24]

Pressure Differences Within the Arterial Tree

As the pressure wave travels from the heart to the periphery, both systolic and pulse pressures increase markedly, whereas diastolic and mean pressures decrease only slightly due to progressive increase in arterial stiffness and to the summated effects of incident and reflected waves. Thus, both systolic and pulse pressures are greater in the arm and leg than in the ascending aorta.[25] The degree of amplification, which can differ widely between individuals, is related to the difference between elastic moduli of the respective arteries and distance to reflection sites.[25] Therefore, brachial artery (cuff) BP is not always a reliable measure of ascending aortic pressure and thus is not always a good predictor of left ventricular (LV) afterload and LV mass, which is an independent predictor of heart failure and coronary heart disease–related mortality.[26] Recent studies have shown that central artery pulse pressure is a better predictor of carotid intima-media thickness,[27] restenosis after coronary angioplasty,[28] coronary artery disease severity,[29] and mortality in end-stage renal disease.[30] Moreover, the beneficial reduction in ascending aortic systolic and pulse pressures with vasodilator drugs is often underestimated by cuff measurements of brachial artery pressure.[31,32] This disparity is due to amplitude and timing of reflected pressure waves from the periphery.[33,34]

Central Artery Pressure Waves

Figure 1 (top) depicts a high-fidelity aortic pressure wave (synthesized from the radial artery pressure wave using a generalized transfer function), with pulse or amplitude ($P_s - P_d$) determined by the interaction of a LV ejected forward-traveling "incident" wave (amplitude, $P_i - P_d$) and a late-arriving reflected wave (amplitude, $P_s - P_i$) from the lower body. The characteristics of the incident wave depends largely upon the elastic properties of the central aorta and is not influenced by wave reflections.[25,33] The characteristics of the reflected wave depends on a more complex set of determinants, namely, the elastic properties of the entire arterial tree (elastic plus muscular arteries and, to a lesser extent, the arterioles), PWV, the round-trip travel time (Δt_p) of the wave from the heart to the periphery and back, and the distance to the major reflecting sites.[25,33]

Aortic augmentation index (AI_a) is related to arterial properties via changes in PWV. Increased arterial stiffness increases PWV and causes early return (ie, Δt_p decreases) of the reflected wave from peripheral reflecting sites to the heart during systole when the ventricle is still ejecting blood.[34] As Δt_p decreases, reflected wave amplitude ($P_s - P_i$) increases and systolic duration (Δt_r) of the wave increases. This mechanism augments ascending aortic systolic and pulse pressures, an effect that increases arterial wall stress, potentiates the development of atherosclerosis, elevates LV afterload, and increases LV mass and oxygen demand while decreasing stroke volume.[34] Because this wave reflection–associated boost in pressure does not contribute positively to ejection of blood, the effect of the extra workload is wasted (pressure) energy ($2.09\Delta t_r[P_s - P_i]$) the ventricle must generate to overcome this augmented aortic pressure.[35] Accordingly, optimal treatment for high central systolic and pulse BP (cardiac afterload) should focus not only on increasing arteriolar caliber and reducing peripheral resistance but also on arterial stiffness, PWV, wave reflection characteristics, and LV wasted energy.[36,37] Correct calculation of these variables (that is, augmentation index, incident and reflected wave amplitude and travel time, distance to reflection sites, and wasted LV energy) depends on the accurate determination of the inflection point (P_i).[25,33]

Peripheral Artery Pressure Waves

The shape of peripheral artery pressure waves are also influenced by arterial stiffness, PWV, and wave reflections (Fig. 1, bottom).[25,38] The radial artery pressure wave is composed of three waves: an incident wave generated by blood flow and two reflected waves, one from the hand region and a later-arriving wave from the lower body. The radial artery augmentation index (AI_r) is defined[39] as P_2/P_1. As the elastic arteries become stiffer, PWV increases and the reflected wave from the lower body returns earlier to the radial artery, migrates up the pressure wave toward peak systolic pressure, and thus causes a decrease[40] in ΔT_{DVP} and an increase in AI_r (Fig. 2, top left). There is a positive relationship between AI_a and AI_r (Fig. 2, bottom), and both can be used as estimates of arterial stiffness.[22,40] However, care must be taken when interpreting interindividual differences in the augmentation index or in using it as an index of arterial stiffness because of its dependence on both heart rate[41,42] and body height.[43]

Pressure Dependence of Arterial Stiffness

Elastic properties of the arterial wall are highly pressure dependent. At low levels of arterial pressure, wall stress is supported by compliant elastin fibers, whereas at higher levels of pressure, wall stress is supported by much stiffer collagen fibers.[25] An increase in elastic artery stiffness is related to arterial wall composition and occurs over a long period, for example, with advancing age, hypertension, and arteriosclerosis. Acute changes can occur in elastic arteries with changes in distending pressure, but these changes are passive. For example, during vasodilation, both pressure and diameter decrease in elastic arteries, causing a passive decrease in wall stiffness and a decrease in PWV. A change in stiffness of muscular arteries is

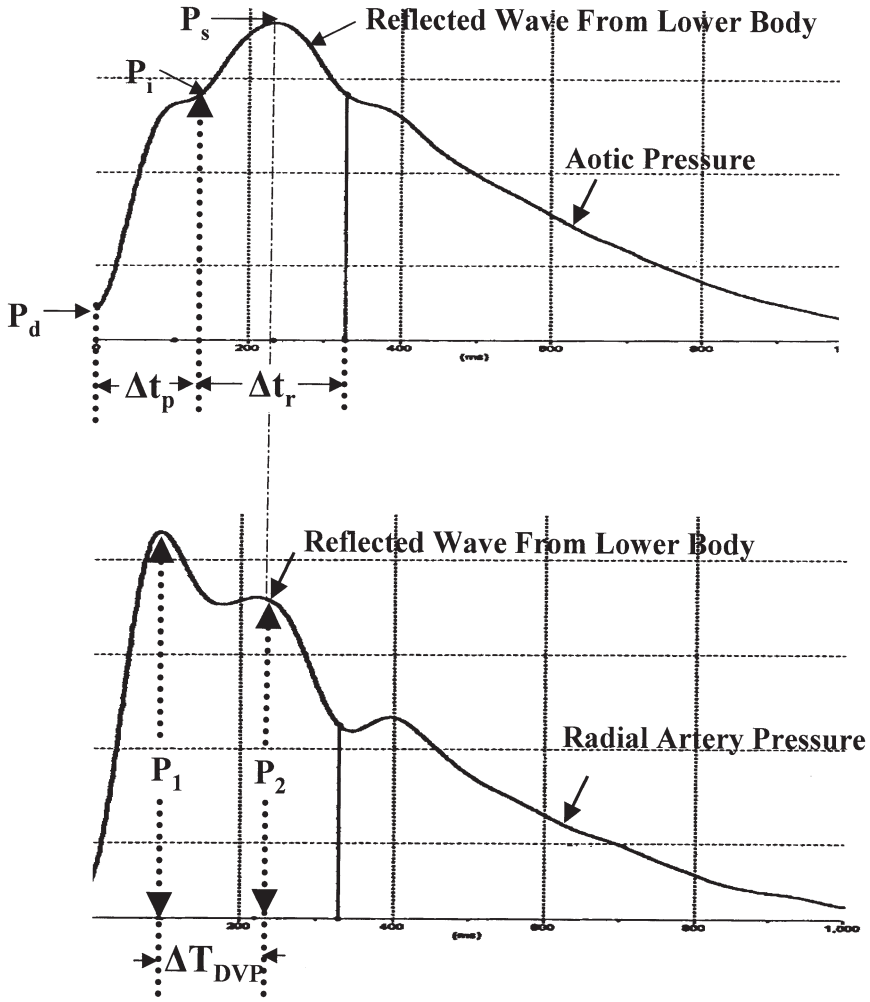

FIG. 1 Top Aortic pressure wave synthesized from the measured radial artery pressure wave (applanation tonometry) using a generalized transfer function. The abbreviation P_s indicates peak systolic pressure; P_i is an inflection point that indicates the beginning upstroke of the reflected pressure wave; P_d is minimum diastolic pressure; Δt_p is the round trip travel time of the forward (or incident) wave from the ascending aorta to the major reflecting site and back; and Δt_r is the systolic duration of the reflected pressure wave. Pulse pressure is $(P_s - P_d) = (P_i - P_d) + (P_s - P_i)$. Augmentation index $(AI_a) = (P_s - P_i)/(P_s - P_d)$ and wasted LV pressure energy $(E_w) = 2.09\Delta t_r (P_s - P_i)$. (**Bottom**) Noninvasive high-fidelity recording of the radial artery pressure wave. The wave has been shifted leftward to align with the aortic pressure wave. The variations in the pressure wave, like those of the aortic pressure wave, are due to wave reflections from the lower body superimposed on the wave. The abbreviation P_1 is the sum of the incident (ejected) wave and reflected wave (from hand); P_2 is the peak of the reflected wave from the lower body minus end-diastolic pressure; P_2/P_1 is the radial artery augmentation index (AI_r); and ΔT_{DVP} is the difference between the first two peaks of the pressure wave and has been used as a measure of arterial stiffness.

primarily due to acute changes in smooth-muscle tone. During vasodilation, diameter increases whereas pressure decreases,[34] causing a decrease in arterial stiffness and PWV; vasoconstriction increases stiffness and has the opposite effect. Advancing age and hypertension have little effect on stiffness of muscular arteries in humans, and drugs have little effect on stiffness of elastic arteries.[25,44]

Aging and Hypertension: Effects on Arterial Stiffness and Wave Reflections

With the passage of time, the walls of systemic arteries undergo certain histologic changes. These changes occur independently of alterations attributed to atherosclerosis. The principal changes with age occur in the arterial intima (which undergoes hyperplasia) and the media. In the load-bearing media, the elastic fibers and laminae lose the orderly arrangement seen early in life and display thinning, splitting, fraying, and fragmentation. The age-related thinning and fragmentation of elastin and the increase in collagen are not seen in muscular arteries. Collagen in the human aorta is much stiffer (at least 500 times) than elastin, and it more than doubles in content from age 20 to 70 years.[25] As a result, age and hypertension are associated with alterations in the elastic properties of the arterial wall that cause profound changes in arterial pressure waves, including increases in both radial artery (Fig. 2, upper left) and aortic augmentation (Fig. 2, upper right) indi-

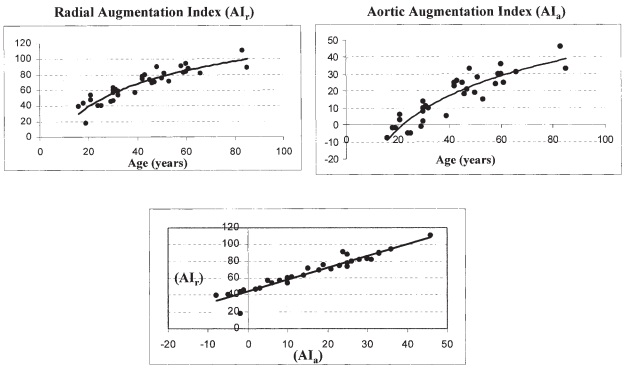

FIG. 2 Age-related changes in radial (**left**) and aortic (**right**) augmentation indices (%) and their relationship (**bottom**).

ces. These changes are attributed primarily to the changes in amplitude and timing of pulse wave reflections from peripheral reflecting sites in the lower body.

Age is an important determinant of arterial wave reflection characteristics.[25,33] In youth, the reflected wave occurs in diastole in both the radial artery and aorta (Fig. 3, top) and aids coronary artery and myocardial perfusion, but with increasing age (Fig. 3, middle and bottom), the elastic arteries stiffen, increasing PWV and causing the reflected wave to occur in systole with greater amplitude and systolic duration. This modification in wave reflection characteristics causes a decrease in stroke output and a corresponding decline in coronary artery perfusion pressure. Radial and aortic systolic pressures increase whereas diastolic pressure increases to middle age (Fig. 3, middle) and then decreases (Fig. 3, bottom).[45] In the three individuals shown in Fig. 3, pulse pressure in the radial artery doubled, whereas pulse pressure in the ascending aorta tripled, causing amplification (brachial/aortic pulse pressure) to decrease from 1.7 to 1.1. Migration of the reflected wave (leftward in Fig. 3) into systole increased both radial

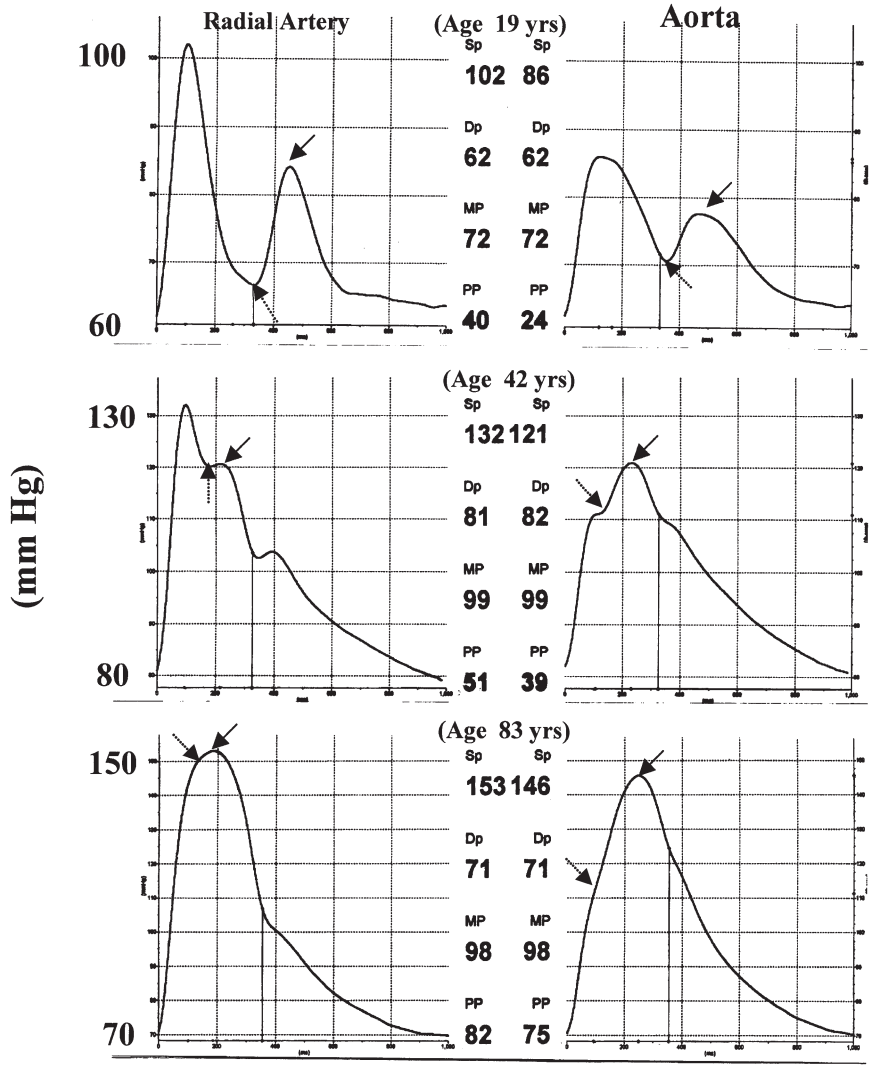

FIG. 3 Noninvasive recordings of radial artery pressure waves (**left**) and synthesized aortic pressure waves (**right**) in three healthy individuals to illustrate the age-related changes in wave reflection characteristics and pressure wave shapes. **Solid arrows** identify the peak of the reflected waves, and **broken arrows** indicate the beginning upstroke of the reflected waves (see text for explanation).

artery and aortic augmentation indices (see Fig. 2). Δt_p decreases, whereas Δt_r increases causing wasted LV pressure energy to increase from 0.0 to 16.3 $\times$ 10^3 dyne-sec/cm^2.

Wave reflection characteristics are amplified in patients with systemic hypertension. An increase in aortic stiffness alone only causes an increase in aortic pulse pressure (for a given stroke volume), with little change in wave contour. Major changes in wave contour are due to alterations in amplitude and timing of wave reflections. Increased arterial stiffness is likely due to several entities occurring simultaneously over a long period. These include decreased elastin, increased collagen, increased calcium content of the arterial wall, increased plasma creatinine and norepinephrine, decreased β-receptor tone of smooth-muscle cells, decreased release of nitric oxide, and increased release of endothelin.

Changes in physical properties of the arterial tree are probably accelerated in some individuals because of adverse lifestyle aspects such as smoking,[46] overeating,[47] and excess alcohol consumption,[48] thereby causing an abnormal increase in arterial stiffness, pulse pressure, and systolic stress. Left ventricular afterload, ascending aortic and radial artery pulse pressures, and augmentation indices are increased by arterial stiffening and increased wave reflection amplitude, all of which are alterations associated with aging and hypertension,[25,44] LV hypertrophy,[49,50] and arterial wall damage—major cardiovascular, cerebrovascular, and renovascular risk factors.[51]

Effects of Pharmacologic Intervention on Arterial Stiffness and Wave Reflections

The long-term beneficial effects of lowering arterial BP on cardiovascular events (eg, myocardial infarction, stroke, and mortality) have been well documented in large clinical trials in both hypertensive[31,32,52–56] and normotensive patients.[57,58] When initiating antihypertensive or BP-lowering drug therapy, an optimal BP should be targeted. However, it must be realized that aggressive BP reduction can, at least theoretically, be detrimental to central and peripheral organ perfusion, particularly in the setting of severe coronary artery disease.[8,34,50] In general, however, lower BP is associated with better outcome. Although brachial BP $\geq$140/90 mm Hg is the standard definition of hypertension,[59] a recent meta-analysis has confirmed that a brachial pressure of 115/75 mm Hg is associated with the lowest mortality rate and that the mortality rate doubles with each 20/10 mm Hg increment in brachial BP.[60]

Different vasodilator drugs have different effects on arteries and arterioles.[61] Arteriolar vasodilators primarily increase arteriolar caliber and therefore decrease peripheral resistance and mean arterial pressure via their action on arteriolar smooth-muscle cells. Arterial vasodilators primarily relax smooth muscle cells in muscular arteries and therefore decrease PWV, wave reflection amplitude and duration, and reduce central systolic and pulse pressures more than brachial cuff pressure components.[25,31–35] Currently available vasodilator drugs have little direct action on elastic arteries, and although drugs are being developed to directly reduce elastic artery stiffness directly, none are currently available for routine clinical use.

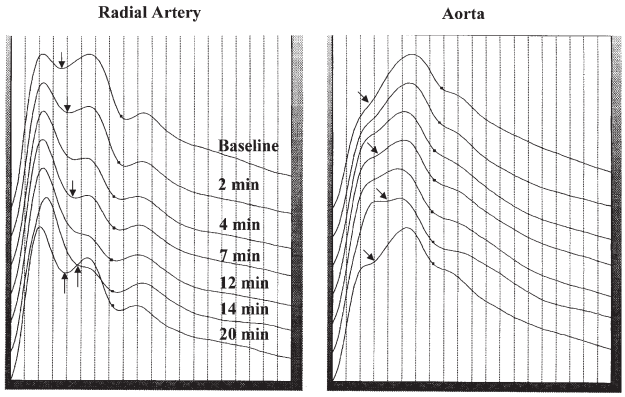

FIG. 4 Radial artery (**left**) and aortic (**right**) pressure waves in a 63-year-old man before (baseline) and after sublingual nitroglycerin (0.4 mg). **Arrows** indicate the beginning upstroke of the respective reflected wave. This vasodilator decreases PWV and delays (rightward shift of the wave) the arrival of the reflected wave in the aorta and radial artery, thus decreasing its amplitude and causing a marked decrease in aortic systolic and pulse pressures. The AI_r decreased from 100% to 53%, whereas AI_a decreased from 32% to 3.0%. Abbreviations as in Fig. 1.

Acute reduction in augmentation index can be achieved by drugs that actively dilate muscular arteries accompanied by the passive affects on elastic arteries.[34] These separate actions decrease pressure wave (incident and reflected) propagation along the entire arterial tree and improve wave reflection characteristics. Vasodilator drugs such as ACEI, ARB, calcium channel blockers, nitrates, phosphodiesterase type 5 inhibitors, nitric oxide, and omapatrilat decrease arterial stiffness and PWV and thus reduce wave reflection via delayed return of the reflected wave from the periphery to the heart while decreasing its amplitude and systolic duration.[31–35] Morphologically, the reflected wave (second pressure peak) on the radial pressure wave migrates rightward and down. These modifications of reflected wave characteristics reduce central systolic and pulse pressure, augmentation index (radial and aortic), and wasted pressure energy, which leads to regression of LV hypertrophy.[56,58] The effects of vasodilator drugs on brachial and radial artery systolic and pulse pressures are much less pronounced than their effects on central artery pressure. This is illustrated in Fig. 4, which shows a patient's response during sublingual administration of nitroglycerin.

Differences in central and peripheral pressure-lowering effects by vasodilator drugs, as illustrated in Figs. 4 and 5, strongly suggest that the beneficial cardiac effects of vasodilator drugs has been grossly underestimated in studies that measure brachial artery cuff BP with no central pres-

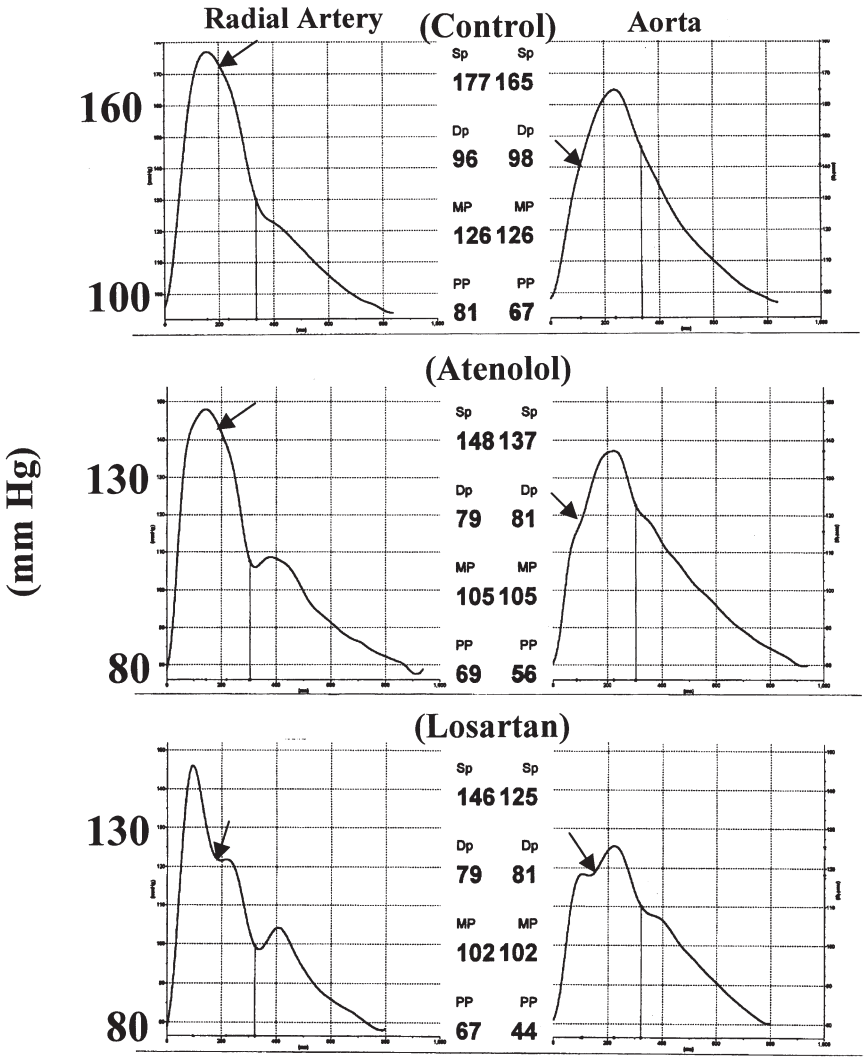

FIG. 5 Noninvasive recordings of radial artery pressure waves (**left**) and synthesized aortic pressure waves (**right**) illustrate the different effects of a β-blocker (atenolol) and an angiotensin receptor blocker (losartan) on central and peripheral arterial pressure wave shapes in a hypertensive patient. **Arrows** denote the beginning of the reflected wave. The waves are scaled to the pressures published in the Losartan Intervention For Endpoint Reduction in Hypertension study (LIFE) trial (see text for explanation).

sure determination. In the Regression of Arterial Stiffness in a Controlled Double Blind Study (REASON) trial,[31,32] the ACEI perindopril decreased synthesized aortic systolic and pulse pressures significantly more than the β-blocker atenolol even though the drugs lowered elastic artery PWV by the same amount. Based upon the above observations, the apparent "pressure-independent" benefits of vasodilator drugs in clinical trials such as the Heart Outcomes Prevention Evaluation (HOPE) trial[57] may accrue in large part to unmeasured but significant reductions in central (but not peripheral) systolic and pulse pressures. Accordingly, it would be expected that the beneficial effects of ACEI, including regression of LV hypertrophy,[58] are not really independent of changes in arterial BP simply, that the sphygmomanometer method does not measure the "right" BP (that is, the pressure the heart pumps against). The same reasoning can easily explain why the ARB losartan was more effective than atenolol in reducing LV mass and cardiovascular mortality in the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study.[55,56] In the LIFE trial, atenolol and losartan reduced brachial systolic and pulse pressure the same amount. However, as illustrated in Fig. 5, atenolol reduced aortic systolic and pulse pressure 28 and 11 mm Hg, respectively, whereas losartan reduced aortic systolic and pulse pressure 40 and 23 mm Hg, respectively. Atenolol had little effect on radial and aortic augmentation indices, whereas losartan had a marked lowering effect.

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