

REVIEW ARTICLE

Pulse Pressure—A Review of Mechanisms and Clinical Relevance

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The goal of this study was to review the origin, clinical relevance and treatment of pulse pressure (PP). Elevated PP is increasingly being recognized as a risk factor for cardiovascular, particularly coronary, disease. Pulse pressure is discussed in terms of both Windkessel and distributive models of the arterial circulation. Pulse pressure arises from the interaction of cardiac ejection (stroke volume) and the properties of the arterial circulation. An increased stiffness of the aorta and large arteries leads to an increase in PP through a reduction in arterial compliance and effects on wave reflection. A number of factors are known to influence arterial wall behavior and, therefore, PP. In addition to the effects of aging and blood pressure on arterial wall elasticity, there is some evidence that atherosclerosis, per se, amplifies these effects. Thus, the relationship between PP and coronary disease may be bidirectional. A number of dietary and lifestyle interventions have been shown to modify large artery behavior. These include aerobic exercise training and consumption of n-3 fatty acids. Conversely, strength training is associated with an increase in arterial stiffness and a higher PP. The effects of antihypertensive medication have been extensively studied, but many studies are difficult to interpret because of concomitant change in blood pressure, and to a lesser degree, heart rate. However a number of studies do suggest direct arterial wall effects, particularly for angiotensin-converting enzyme inhibitors. A distributed compliance model of the arterial circulation provides a framework for understanding the causes, effects and potential treatment of elevations in PP. (J Am Coll Cardiol 2001;37:975–84) © 2001 by the American College of Cardiology

Pulse pressure (PP) arises as a consequence of the episodic nature of cardiac contraction and the properties of the arterial circulation. Thus, while mean arterial pressure is adequately described by cardiac output and total peripheral resistance, the origins of PP are more complex. As such, PP is not explicable by any single, simple model of the circulation. In this review, PP will be discussed in terms of a synthesis of two complementary model systems, namely the well-known Windkessel model and one based on the propagative properties of the arterial circulation.

In its simplest, two-element form, the Windkessel model describes the circulation in terms of parallel resistance and capacitance components. The resistance element corresponds to measured peripheral vascular resistance, while the capacitance element corresponds to the compliance (C) of the arterial circulation. Compliance is simply a measure of the capacity of a volume-containing structure, in this case the arterial system, to accommodate further increases in volume (Δ volume/ Δ pressure). While C is widely distributed throughout the arterial tree, total systemic arterial C is predominantly determined by the aorta (1) and its major branches (Fig. 1). Arterial C can be estimated from the decay in diastolic pressure (2) as well as by the simpler

approach of: $C = \text{stroke volume (SV)}/\text{PP}$, and studies have suggested reasonable correspondence between these methods (3,4). An important feature of the arterial system is that its C is dependent on initial loading conditions such that it becomes less at higher pressures. This has important consequences not only in terms of the Windkessel model but also in terms of the transmission or propagative properties discussed subsequently. It is apparent from the approximation $C = \text{SV}/\text{PP}$ that elevation of PP can be secondary to a rise in SV or a fall in C. The rise in PP (or systolic pressure) with age in healthy subjects (5) relates to falls in C, whereas elevation of PP in the young appears to be related to increases in SV (6).

Analysis solely in terms of the Windkessel model is limited because this model lumps the arterial tree into the entities C and resistance, assuming that all pressure changes occur instantaneously, whereas the circulation serves to distribute cardiac output through a series of branching networks. Hence, the Windkessel model is unable to explain phenomena pertinent to a distributed system, such as wave reflection and frequency dependence. This is of particular importance in the understanding of PP. Wave reflection occurs throughout the arterial tree at each branching of arteries: a fraction of the forward travelling pulse wave is reflected back towards the heart, where it summates with the forward travelling wave. Frequency, distance and vessel wall-dependent dampening occur of both the forward and the backward travelling wave. Hence, not surprisingly,

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Abbreviations and Acronyms

- ACE = angiotensin-converting enzyme
- C = compliance
- DBP = diastolic blood pressure
- LV = left ventricle or left ventricular
- PP = pulse pressure
- PWV = pulse wave velocity
- SBP = systolic blood pressure
- SV = stroke volume

reflected waves returning to the heart originate predominantly at the major branches of the aorta and its terminal tapering (7) (Fig. 1). This is due to the proximity of these points to the heart, resulting in reduced dampening and in the amount of reflection, which, among other determinants, relates to the amount of change in vessel diameter at a branching site.

The correspondence of forward and backward waves will also be determined by their respective timing at any given point of measurement. Augmentation of central systolic pressure refers to the superposition of a visible reflected wave onto the forward travelling wave generated by left ventricular (LV) ejection. This superposition is often noticeable as an inflection on the aortic pressure trace, and it may lead to an increase in systolic pressure (and, hence, PP) over and above that generated by LV ejection alone. Peripherally, PP amplification refers to the phenomenon wherein the PP measured at a peripheral artery is amplified vis-a-vis that present in the proximal aorta. Although this amplification is lower for the brachial than it is for the femoral artery and lower in older as compared with younger age groups, it is important to note that peripheral estimates of PP are not identical to measured central PP.

Pulse pressure, thus, depends on LV ejection and the properties of the arterial wall, which determine both the C and the transmission characteristics of the arterial system.

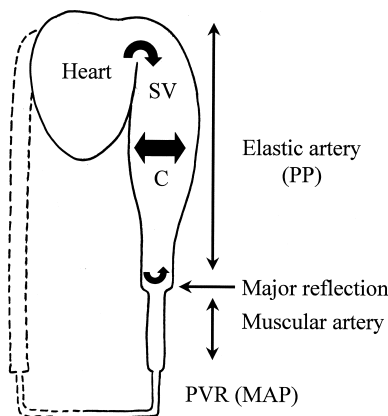


Figure 1. Pulse pressure (PP) arises from the interaction between stroke volume (SV) and the characteristics of the arterial circulation that determine compliance (C) and wave reflection. As discussed in the text, wave reflection occurs at multiple sites but is shown in the diagram as a single site for the sake of simplicity. Cardiac output and peripheral vascular resistance (PVR) determine mean arterial pressure (MAP).

While the advantage of the two-element Windkessel model is its simplicity, including the ability to describe the arterial system through simple numbers, that is, C and resistance, it fails to characterize other important determinants. Considering the arterial system as comprising a distributed C overcomes these limitations to a large extent. However, as both relate to the same fundamental, that is, the properties of the arterial wall, both approaches may be appropriate depending on circumstances.

PP and anthropometric factors. EFFECTS OF AGE, GENDER, HEIGHT, HEART RATE. Aging is associated with a loss of elasticity in the aorta and major arterial conduits. The increase in large artery, particularly aortic, stiffness resulting from fragmentation and disruption of elastic lamellae and alteration in the collagen to elastin ratio is of profound importance to the genesis of increased PP with age (5,8,9). The consequences of this increase in stiffness are important in both Windkessel and propagative models of the circulation by leading to both reduced arterial C and increased pulse wave velocity (PWV). Reduced C will increase PP due to a reduced “buffering” capacity available from the arterial wall while the concomitant increase in PWV will increase systolic pressure augmentation, as discussed in more detail in the following text.

Loss of arterial elasticity, in the absence of compensatory dilation, will both reduce arterial C and increase the speed of wave transmission due to the dependence of the latter on vessel wall properties as given in the Bramwell-Hill and Moens-Korteweg equations (10-12). The latter effect will lead to earlier return of the reflected pressure wave. Hence, the reflected wave superposes earlier during systole, resulting in increased systolic pressure augmentation, thereby also increasing central PP. Changes in reflection coefficient (i.e., the proportion of forward to backward travelling wave) and the site of major reflection could also contribute to altered magnitude and timing of wave reflection and, therefore, central pressure augmentation. Animal data suggest that age-related increases in atheroma at branch sites could induce changes by these mechanisms, but no evidence is available to support such a proposal in humans (13). The time taken for return of the reflected pressure wave will also depend on distance to principal reflection sites and, hence, on body height. There is ample evidence for a relation between central pressure augmentation and height (14-16). Such a relation could be expected to produce male-female differences, and, indeed, augmentation index is greater in women than it is in men (14-16). Whether there are body-size independent differences is less certain. The central coincidence of forward and backward waves will also depend on the timing of ventricular ejection. Due to the proportionality between ejection time and cardiac cycle duration (17,18), the peak of the forward travelling wave will be relatively delayed at slower heart rates. Thus, even with a fixed reflection site and speed of wave transmission, there will be an altered relationship between forward and backward waves. Central pressure augmentation and, thus,

central PP will, therefore, be amplified at lower heart rates (14). The somewhat faster heart rate found in women will, therefore, to an extent, counteract the effects of shorter stature.

A number of nonpharmacological (19-23) as well as pharmacological interventions (discussed subsequently) have been shown to result in short-term modifications to large artery properties. These appear to be in excess of the effects attributable to change in mean pressure and which operate through the nonlinear characteristics of large artery wall behavior, leading to reduced stiffness at lower pressures. The most plausible explanations for 'direct' arterial wall effects appear to be change in smooth muscle tone leading to alterations in the proportion of load borne by elastic vis a vis nonelastic tissues (24) and changes in the vasa vasorum, which have been shown to affect large artery properties (25,26). Short-term change in functional cross-links could also contribute to this.

EFFECTS OF CHOLESTEROL, DIABETES, HYPERTENSION, HOMOCYSTEINE. A number of pathophysiological states have also been shown to affect large artery properties. Interestingly, elevated cholesterol levels, in the absence of overt atheroma, appear to be associated with reduced, rather than enhanced, aortic stiffness. In a study of asymptomatic subjects with marked hypercholesterolemia, aortic stiffness showed a less steep increase with age than was the case for control subjects (27). Similarly, very young subjects with familial hypercholesterolemia showed more compliant large arteries (28), whereas somewhat older subjects with familial hypercholesterolemia showed reduced large artery C in one study (29) but not another (30). The latter study did not find any relation between standard lipid variables and aortic C, which was, however, reduced with increasing levels of oxidized low-density lipoprotein. Asymptomatic 35-year-old men showed a negative correlation between aortic stiffness and low-density lipoprotein cholesterol (31). A similar situation has been demonstrated in diabetes where very early investigation of young subjects with type I diabetes were found to have increased arterial C, whereas older subjects with type II diabetes (likely to have macrovascular disease) had less distensible large arteries (32). Diabetic subjects appear to be particularly susceptible to the effects of a high salt diet in reducing C (33) but are responsive to fish oils (20). In addition to diabetes, hypertension has also been found to reduce brachial artery distensibility (34). Salt sensitive hypertensive subjects have lower large artery C than those who are salt resistant (35). Although elevated plasma levels of homocysteine have been related to systolic hypertension (36), there appears to be little effect on the stiffness of carotid or femoral arteries (37,38).

PP amplification. Pulse pressure measured at the brachial artery will also be subject to the effects of alteration in large artery properties. Transmission of arterial pressure to the periphery is accompanied by PP amplification. Mechanisms

proposed to account for this include reflection from distal sites (39) as well as nonlinearity in the forward travelling wave from the heart (40). This leads to central-peripheral PP differences that diminish with age due to the effect of arterial stiffening in producing central systolic pressure augmentation (41). The relationship between brachial PP and height suggests that the phenomenon of peripheral pressure amplification is also affected by transmission length (42). Systolic pressure and PP measured at the brachial artery rise with age. Data from the U.S. suggest a greater increase in brachial PP with age in women compared with that in men, but this is not evident in all populations (43).

The phenomenon of PP amplification may have important consequences when considering clinical end point studies (discussed in the following text). The overwhelming majority of these studies have measured pressure at the brachial artery, whereas important pathophysiological consequences of change in PP, such as cardiac hypertrophy and function and coronary perfusion, are related to central pressure. The importance of the disparity between central and peripheral PP is somewhat lessened by its diminution with age, but it is nonetheless important not to ignore its potential impact.

Summary. Arterial (primarily aortic) stiffening, such as occurs with age, increases PP by reducing C and increasing PWV. An increase in PWV leads to earlier return of the reflected wave with systolic pressure augmentation. A rise in mean blood pressure will operate similarly to increase PP due to the nonlinear stress-strain behavior of the arterial wall, leading to increased stiffness at higher distending pressures. Changes in the coincidence of forward and backward travelling waves underlie the effects of height and heart rate, with short stature and slow heart rate both favoring systolic pressure augmentation and increased PP. Comparison of PP between populations or study groups need consideration of these anthropometric factors including the effects of PP amplification at peripheral sites.

Surrogate and end point clinical studies. A number of studies have investigated relationships between PP and surrogate end points such as vascular structure and LV hypertrophy. Measures of PP have included conventional brachial sphygmomanometry, ambulatory monitoring, including intra-arterial pressure recording and site specific measures of PP, including those obtained noninvasively by tonometry. To date, little information is available to relate central pressures to clinical end points. An important consideration in interpreting studies on PP and clinical and surrogate end points is the extent to which the effects of PP can be shown to be independent of the effects of other blood pressure terms, particularly mean pressure.

Surrogate end points. Increases in clinic and ambulatory PPs were the only significant predictors of wall thickness/lumen ratio in subcutaneous arterioles harvested from skin buttock biopsies of normotensive and hypertensive subjects (44). Both PP terms remained independently significant in the presence of age and other clinic blood pressure terms. In

a study of hypertensive subjects, those with PP ≥ 60 mm Hg had higher values for LV mass than those with PP ≤ 60 mm Hg, despite similar mean pressures (45). In a cross-sectional study of normotensive and untreated hypertensive subjects, carotid intima-media thickness was related to carotid, but not to radial, PP or to mean pressure (46). In a nine-month study of patients with essential hypertension treated with either an enalapril- or celiprolol-based treatment regimen, the change in carotid intima-media thickness was related to the fall in central pulse but not mean pressure (47). In a study of patients undergoing 24-h intraarterial blood pressure monitoring on the basis of elevated clinic pressures, both carotid intima-media thickness and LV mass index were related to baseline PP after an average follow-up of more than nine years (48). In this study, relations were evident between these end points and both intraarterial brachial systolic blood pressure (SBP) and PP, but not diastolic blood pressure (DBP) (48). In postmenopausal women, carotid intima-media thickness has been related to the elevation in PP produced by mental stress (49). In an eight-year follow-up study of women traversing menopause, baseline SBP, but not DBP, was predictive of increases in both coronary and aortic calcium scores (50). Regression of LV hypertrophy by pharmacological treatment in spontaneously hypertensive rats was dependent on changes in pulsatile load, despite similar effects on mean pressure (51).

Clinical events. Despite finding a positive association between PP and electrocardiogram abnormalities in a cross-sectional study, a Chicago Heart Association and Health Department study failed to find a relation between PP and subsequent mortality (52-54). However, a number of other studies have found positive associations between PP and a range of subsequent cardiovascular clinical end points. In the Framingham Study, while SBP, DBP and PP were all positively related to outcome when entered individually, when entered in combination the association was negative for DBP, with PP being at least as good a predictor as the other terms for the middle-aged and elderly (55,56). In the Boston Veteran's Administration Study of healthy male volunteers aged 21 to 80 years at enrollment, cardiovascular death was related to baseline SBP in younger (< 60 years) subjects, whereas in older (> 59 years) subjects PP appeared to be a more accurate predictor of death than SBP or DBP (57). In a 10-year follow-up of $> 13,000$ Dutch women aged ≥ 50 at baseline who were participating in a breast screening program, baseline SBP was positively and monotonically related to stroke and total mortality (58). However, the relation between SBP and subsequent coronary events and cardiovascular mortality was J shaped, with an apparent increase at lower SBP levels (58). In a noninvasive 24-h ambulatory study of initially untreated subjects with essential hypertension, both baseline SBP and PP were related to cardiovascular events and mortality over a mean follow-up of 3.8 years with a stronger relationship for ambulatory compared with clinic pressures (59). In the Medical Re-

search Council (MRC) mild hypertension trial, combined fatal and nonfatal myocardial infarcts were related to baseline PP (and SBP), whereas mean arterial pressure was a better predictor of stroke (60). In a study of $> 19,000$ men initially aged 40 to 69 years, brachial PP was a predictor of cardiovascular mortality over a mean follow-up of 19.5 years. Importantly, this association was evident at both low and high mean pressure (61). In the Studies Of Left Ventricular Dysfunction (SOLVD) study of patients with impaired LV function in which more than 70% had had a previous myocardial infarction, baseline brachial PP was a predictor of total and cardiovascular mortality and remained so in multivariate analysis even after adjustment for mean pressure and a range of other covariates (62). In contrast, with such adjustment, baseline mean pressure showed a significant inverse relation with total and cardiovascular mortality. In the Systolic Hypertension in the Elderly Program (SHEP) of elderly subjects with isolated systolic hypertension, both stroke and total mortality were related to increased PP at baseline independent of mean pressure (63). In the East Boston senior health project, baseline brachial PP was an independent predictor of congestive heart failure in male and female subjects > 65 years who were free of congestive failure at baseline and who were followed for an average of 3.8 years (64).

Summary. Pulse pressure has been related to a number of surrogate end points such as LV hypertrophy, and, in addition, baseline PP has been found to be predictive of subsequent cardiovascular, particularly coronary, events. Of particular importance is the finding in several studies that PP is as good or better a predictor than other blood pressure terms.

Intervention studies. Intervention studies have not been specifically designed to address the question of PP. However, there have been studies with isolated systolic hypertension as the entry criterion. Since such studies have required normal diastolic pressures, they have inevitably included subjects with elevated PPs. In the Systolic Hypertension in Europe study with the calcium channel blocker nitrendipine, there was a significant reduction of 41% in stroke and a reduction of 26% in combined coronary events (65). In the SHEP trial, there was a reduction of 36% in stroke and 27% in combined coronary events (66). The Systolic Hypertension in China study of isolated systolic hypertension in the Chinese community also reported significant reductions in both stroke and combined coronary and sudden deaths (67-69). A recent meta-analysis found that active treatment in patients aged ≥ 60 with SBP ≥ 160 mm Hg and DBP ≤ 95 mm Hg reduced stroke by 30%, coronary events by 23% and total mortality by 18% (70).

Bidirectionality-elevated PP as cause and effect. While there is substantial evidence linking an elevated PP to adverse cardiovascular outcomes, there has been little study of possible mechanisms linking PP to cardiovascular pathology. Pulse pressure elevation was shown to induce endothelial dysfunction as assessed by acetylcholine reactivity (71) in

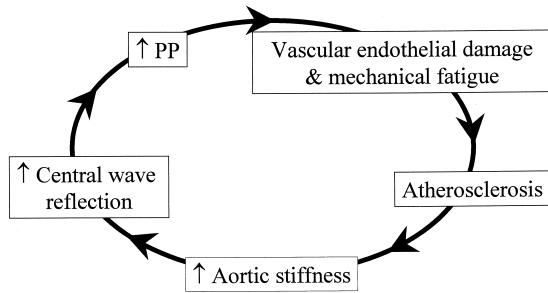


Figure 2. Schematic diagram illustrating the concept of bidirectionality in the relationship between pulse pressure (PP) and atherosclerosis. Elevated PP promotes vascular damage, an antecedent to atherosclerosis, which results in large-vessel stiffening and increased wave reflection, thus, further amplifying PP. While it is not clear which is the incipient event in this cycle, it is clear that, once initiated, a vicious cycle promoting disease progression ensues.

small vessels, and endothelial dysfunction is a possible antecedent of atherosclerosis. As discussed, PP has also been related to LV hypertrophy. A possible additional explanation for the relationship between PP and cardiovascular end points is provided by the concept of bidirectionality—that is, an elevated PP is both a cause and a consequence of atherosclerosis (Fig. 2). Thus, if atheroma were widely distributed throughout the arterial system at an early, presymptomatic stage and if the presence of such atheroma led to increased large artery stiffness, this could result in a statistical association between baseline PP and future clinical events. Such a proposition requires evidence that atherosclerosis is indeed associated with large artery stiffness, as discussed in detail in the following text. Although such evidence cannot prove that aortic stiffness would have been increased at an earlier stage in the disease process, a recent outcome study found that aortic stiffness at baseline, as measured by PWV, was predictive of both all-cause and cardiovascular mortality, even with adjustment for other risk factors, indicating a prognostic role for aortic properties per se (72).

Atherosclerosis and large artery stiffness. It is recognized that coronary atheroma is often accompanied, even at an early phase, by disease in other large vessels, particularly the thoracic and abdominal aorta (73,74). Indeed, one explanation for the observed relationship between elevated inflammatory risk markers such as C-reactive protein and future coronary events (75) can be that such elevation is a marker of a widespread atheromatous process. The aorta and major arteries are known to stiffen with age, but several studies have found that the presence of widespread atheroma amplifies this effect. Thus, measurements of the stiffness of the aorta in the proximal ascending aorta, the aortic arch and the abdominal aorta have all been shown to be elevated in patients with coronary disease (27,76–78). Similarly, arterial C, largely contained within the aorta, has been shown to be significantly lower in such patients (79). Negative studies have also been reported, but these have not identified subjects on the basis of presentation with clinical coronary disease. In a study of asymptomatic men, there was

no relationship between aortic C, estimated from PWV, and coronary calcification (80), determined by ultra-fast computed tomography. Compliance adjusted for mean arterial pressure did, however, correlate negatively with the number of extra-coronary disease sites, but only before adjustment for the effects of age. As discussed, it has become clear in recent years that coronary events are more closely predicted by systolic and PP, both consequences of increased arterial stiffness, than by diastolic pressure (61,81). In a recent study, we were able to show that the elevation in PP in subjects with coronary disease was closely associated with an increase in echocardiographically measured aortic stiffness (77).

The demonstration of an association between aortic properties and atherosclerotic, including coronary, disease cannot, per se, be informative about the direction of causality. Thus, it is possible that a rise in PP due to degenerative changes (8) is an initiating event in the subsequent development of atherosclerosis. Even if this were so, it does not preclude the operation of a “positive feedback” as shown in Figure 2. The damaging effect of PP may itself operate through inducing further, repetitive arterial wall damage. Changes in arterial stiffness can certainly appear early in the development of experimental atherosclerosis (82) and be exacerbated by mechanical damage (83).

Coronary perfusion. An additional phenomenon, which may also restrict the potential benefit from blood pressure reduction, relates to impairment of coronary perfusion. Experimental studies have established that the presence of a stiffened proximal circulation, achieved by bandaging the aorta in vivo, or the use of a stiffened bypass circulation is associated with reduced coronary perfusion, and this is particularly noticeable subendocardially and in the presence of a coronary artery stenosis (84,85). This situation would likely be exacerbated by a treatment-induced reduction in mean pressure. A potential adverse effect of blood pressure reduction has previously been aired in man in relation to the existence of a J-shaped curve relating blood pressure treatment to coronary outcome (86–88). In the recently published Hypertension Optimal Treatment study, there was a trend to increasing cardiovascular mortality for subjects with diastolic pressure reduced to <80 mm Hg, whereas stroke (all) showed a further progressive decline (89).

Summary. Some, but not all evidence, indicates that atherosclerosis, per se, is associated with an increase in aortic stiffness (and a reduced C) over and above that due to aging. Widened PP may exacerbate myocardial ischemia as a result of increased afterload and reduced coronary perfusion.

PP as a therapeutic target. Despite the impressive epidemiological associations between PP and cardiovascular end points and outcomes, it is currently premature to identify reduction of PP, per se, as a therapeutic goal. As indicated in the introduction, PP will fall with any reduction in mean pressure. A more targeted approach to lowering PP, if eventually indicated, will come from an increase in arterial

C. In addition to pharmacological agents, increases in arterial C can be achieved by a variety of nonpharmacological means, such as exercise training (19,90) and dietary manipulations, particularly including n-3 fatty acids (20,22), estrogen compounds (21) and reduced salt intake (91). Hormone replacement therapy in postmenopausal women has been shown to increase arterial C and to lower central (aortic) PP (92-94). All these effects appeared in excess of those predicted from the change in mean pressure. In contrast with the effects of aerobic training, muscle strength training was associated with increased arterial stiffness and increased PP (95).

A number of studies have been carried out to compare the effects of different agents and classes on arterial properties that are relevant to the issue of PP. When considering such studies, a number of additional factors need to be considered. Thus, the nonlinearity of arterial elasticity means that a reduction of distending pressure will, *pari passu*, lead to a reduction in arterial stiffness. There may also be heart rate effects on arterial properties (96,97). An additional consideration in many studies is the location and class of artery under investigation. Thus, many studies have only examined muscular or peripheral arteries, such as the brachial artery, which may not be representative of more proximal vessels. The pathophysiological consequences of change in PP largely relate to change in central, rather than peripheral, pressures.

Angiotensin-converting enzyme inhibitors. In a placebo-controlled crossover study of the acute effects of the angiotensin-converting enzyme (ACE) inhibitor, quinapril, in patients with essential hypertension, there were increases in carotid artery distensibility and aortic C (determined by PWV). Whereas all the effects on the carotid artery could be attributed to effects secondary to blood pressure reduction, the effects on aortic distensibility appeared to be a combination of direct and blood pressure-dependent effects (98). Pulse pressure was reduced by a similar amount at both carotid and brachial sites. In a catheter laboratory study with intravenous captopril, large artery C was lower in hypertensive, compared with normotensive, subjects and was increased by captopril but not to the values found in normotensive subjects (99). In another acute study, neither intravenous dihydralazine nor perindoprilat significantly altered carotid-femoral PWV in patients with mild-moderate hypertension (100). However, while there was a strong correlation between change in blood pressure and PWV in the dihydralazine group, there was no such correlation with perindoprilat, which was interpreted as implying a direct arterial effect of the ACE inhibitor.

Ramipril reduced aortic PWV in hypertensive subjects treated for 42 days. Although blood pressures were lowered, there was no relationship between change in PWV and change in diastolic or mean blood pressure, suggesting a blood pressure independent effect (101). Three months treatment with perindopril increased brachial artery C in comparison with placebo in a single-blind study in hypertensive subjects without changing tangential tension, again

suggesting a direct effect on arterial wall properties (102). In a single-blind, crossover comparison of eight weeks treatment with the ACE inhibitor lisinopril or the calcium channel blocker nifedipine in elderly subjects with essential hypertension, aortic PWV was reduced significantly more by lisinopril, despite there being no difference in their effect on mean arterial pressure, suggesting an arterial wall effect of ACE inhibitors (103).

Calcium channel blockers. In a double-blind, crossover comparison of 12 weeks treatment with the calcium channel blocker felodipine or the diuretic hydrochlorothiazide in subjects with mild-to-moderate hypertension, there were more pronounced falls in PWV at carotid-femoral as well as peripheral sites with felodipine (104). However, felodipine was also associated with greater blood pressure reduction (104). The finding of brachial artery dilation with felodipine, but not hydrochlorothiazide, however, indicated direct arterial wall effects of the calcium channel blocker. Peripheral C, determined by brachial-radial PWV measurement, was improved by the calcium channel blocker nicardipine but not by the beta-adrenoceptor antagonist atenolol in hypertensive subjects treated for eight months (105). In a parallel group comparison of hydrochlorothiazide with nitrendipine in subjects with mild to moderate hypertension treated for two months, there were no significant differences in effects on muscular radial artery C (106). Effects of nitrendipine (as well as perindopril) in hypertensive subjects appeared to be determined by angiotensin II receptor I genotype. Thus, whereas PWV change with perindopril was more marked in those with a C allele, only those with the AA allele showed a PWV effect with nitrendipine (107).

Alpha- and beta-adrenoceptor antagonists. In an acute invasive study in which aortic PWV was inferred from the first minimum of the impedance modulus, PWV was unaffected by beta-adrenoceptor blockade but was reduced by combined alpha- and beta-blockade (108). As discussed, in a comparative study with nicardipine, atenolol did not affect peripheral PWV in long-term treatment of hypertensive subjects (105). However, in another study, atenolol reduced aortic PWV as well as blood pressure (109). In other studies of beta-adrenoceptor antagonists, whereas six weeks treatment with metoprolol had no significant effect on brachial-radial or carotid-femoral PWV in hypertensive subjects (110), four weeks treatment with bisoprolol reduced both peripheral and central PWV (111). In an eight week study in patients with essential hypertension comparing atenolol with the ACE inhibitor fosinopril, augmentation index, a marker of large artery properties, was reduced more by fosinopril than it was by the beta-adrenergic blocking agent (112). However, no adjustment was made for the lower heart rate in the atenolol-treated subjects and, as discussed, augmentation index is known to be increased at slower heart rates.

Diuretics and nitrates. Acute administration of isosorbide dinitrate to untreated hypertensive subjects increased C at brachial, carotid and femoral sites when measured with an

echocardiography tracking device (113). Nitrate therapy also produced a fall in blood pressure and in wave reflection as assessed by central pressure augmentation (113). A single oral dose of nicorandil reduced blood pressure and peripheral PWV in hypertensive subjects (114). In a comparison of a potassium-losing with a potassium-sparing diuretic in hypertensive subjects treated for six weeks, both lowered blood pressure from baseline but did not significantly affect PWV (115).

Despite a considerable body of work, there is still uncertainty over the direct effects of a number of antihypertensive agents on large artery properties. However, a number of studies have suggested that ACE inhibitors and, to a lesser extent, calcium channel blockers do exert direct arterial wall effects and induce changes not solely due to the passive effects of blood pressure lowering. The newer techniques of tonometry and wall tracking do allow examination of arterial wall properties at different pressures, but these studies are limited to accessible (peripheral) arteries, whereas the major contributor to systemic arterial C and, therefore, PP is the aorta, which cannot be studied by these techniques. A promising new approach in assessing central pressure changes is the use of transfer functions to estimate central arterial waveforms and pressures from recordings at peripheral sites (116).

Summary. Since PP elevation is predominantly a consequence of increased large artery stiffness, a targeted effect on PP in excess of that attributable to a reduction in mean pressure would be expected from treatments and interventions that affect large arteries. An effect on large artery properties has been demonstrated for a number of nonpharmacological interventions, including aerobic exercise training and dietary consumption of n-3 fatty acids. Studies of the effects of pharmacological therapy have been somewhat confounded by change in mean pressure (and heart rate), but there is evidence for specific large artery effects, most consistently for ACE inhibitors.

Conclusions. Determinants of PP can be adequately discussed in terms of a model of distributed C, with arterial wall properties determining both C and transmission characteristics. There is now extensive epidemiological evidence for a positive relationship between PP and future cardiovascular events, and some evidence that PP modification, per se, affects cardiovascular end points. However, more evidence is required before it can be firmly concluded that reduction in PP should be a specific therapeutic target. The acquisition of such evidence would be helped by therapies that specifically target PP, rather than mean pressure.

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