Isolated Systolic Hypertension
Prognostic Information Provided by Pulse Pressure

Michael J. Domanski, Barry R. Davis, Marc A. Pfeffer, Mark Kastantin, Gary F. Mitchell

Abstract—Increased arterial stiffness results in increased characteristic impedance of the aorta and increased pulse wave velocity, which increases systolic and pulse pressures. An association between increased pulse pressure and adverse cardiovascular events has been found in normotensive and hypertensive patient populations. Increased pulse pressure has also been associated with thickening of the carotid intima and media. However, the relationship between pulse pressure and stroke has not previously been evaluated. In this study, we examined the hypothesis that pulse pressure is an independent predictor of stroke in elderly patients with systolic hypertension entered in the Systolic Hypertension in Elderly Program. Differences in baseline characteristics were examined by tertiles of pulse pressure. The independent prognostic value of pulse pressure and mean arterial pressure for predicting either stroke or total mortality was assessed with Cox proportional hazards models that included pulse pressure, mean arterial pressure, and other variables that were significant on univariate analysis. This analysis demonstrated an 11% increase in stroke risk and a 16% increase in risk of all-cause mortality for each 10-mm Hg increase in pulse pressure. Each 10-mm Hg increase in mean arterial pressure was independently associated with a 20% increase in the risk of stroke and a 14% increase in the risk of all-cause mortality. These data provide strong evidence of an association of increased conduit vessel stiffness, as indicated by increased pulse pressure, with stroke and total mortality, independent of the effects of mean arterial pressure, in elderly patients with isolated systolic hypertension. (Hypertension. 1999;34:375-380.)

Key Words: pulse pressure ▪ stroke ▪ hypertension ▪ elderly ▪ compliance

The association between hypertension, particularly systolic hypertension, and cerebrovascular disease, including carotid atherosclerosis and stroke, has been established.1 Once thought to be a benign accompaniment of aging, isolated systolic hypertension is now known to increase the risk of stroke and other adverse cardiovascular events. Furthermore, the Systolic Hypertension in the Elderly Program (SHEP) clearly demonstrated that effective treatment of isolated systolic hypertension in elderly patients markedly reduced this risk of stroke.2 Evidence that implicates increased pulse pressure as an independent predictor of stroke in elderly patients with systolic hypertension entered in the Systolic Hypertension in the Elderly Program. Differences in baseline characteristics were examined by tertiles of pulse pressure. The independent prognostic value of pulse pressure and mean arterial pressure for predicting either stroke or total mortality was assessed with Cox proportional hazards models that included pulse pressure, mean arterial pressure, and other variables that were significant on univariate analysis. This analysis demonstrated an 11% increase in stroke risk and a 16% increase in risk of all-cause mortality for each 10-mm Hg increase in pulse pressure. Each 10-mm Hg increase in mean arterial pressure was independently associated with a 20% increase in the risk of stroke and a 14% increase in the risk of all-cause mortality. These data provide strong evidence of an association of increased conduit vessel stiffness, as indicated by increased pulse pressure, with stroke and total mortality, independent of the effects of mean arterial pressure, in elderly patients with isolated systolic hypertension. (Hypertension. 1999;34:375-380.)

An association between increased pulse pressure and adverse cardiovascular events, presumably due to a detrimental influence of increase in stiffness of the conduit vessels, has been demonstrated in normotensive and hypertensive patient populations17–21 as well as in patients with reduced left ventricular function.15,16 This adverse association has been shown to be independent of age, mean arterial pressure (MAP), and other covariates thought to influence pulse pressure or outcome in patients with cardiovascular disease. Although a recent population-based study speculated that increased pulse pressure may help to explain the higher incidence of stroke in patients

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375
with isolated systolic hypertension as opposed to those with diastolic or mixed systolic/diastolic hypertension, the direct relationship between pulse pressure and stroke has not been established. The present study examined the association of pulse pressure and stroke as well as total mortality in patients randomized into SHEP.

Methods
The SHEP trial was a randomized, controlled study of the effectiveness of antihypertensive drug treatment in the prevention of stroke in 4736 people with isolated systolic hypertension. Blood pressure readings at the first and second baseline visits were averaged to establish a baseline blood pressure for each participant. Treatment goals were established on the basis of this baseline blood pressure as previously described in detail. Initial therapy was chlorthalidone, which was followed by atenolol or reserpine as needed. Pulse pressure was calculated as the difference between baseline and prerandomization SBP and DBP. MAP was calculated according to the formula MAP = (2 × DBP + SBP)/3. Fatal or nonfatal stroke, according to previously described criteria, was the primary end point of SHEP.

Statistical Methods
Differences in baseline characteristics by tertile of pulse pressure were evaluated by ANOVA for continuous variables and by a test for linear trends for categorical variables. Baseline variables, including randomization assignment, age, pulse pressure, MAP, SBP, DBP, heart rate, race, gender, body mass index, educational attainment, serum uric acid, HDL cholesterol, hematocrit, current smoking status, history of intermittent claudication, presence of carotid bruits, history of cardiovascular disease, presence of ECG abnormality, presence of left ventricular hypertrophy by ECG criteria, history of stroke, history of diabetes, alcohol consumption ≥1 drink per week, and history of myocardial infarction, were evaluated as predictors of stroke and total mortality with a Cox proportional hazards model. All univariate predictors associated with an end point (P < 0.10) were included in a preliminary multivariate analysis. Those that remained significant (P < 0.10) were included in the final models along with pulse pressure and MAP.

Results
Higher pulse pressure was associated with both an increase in SBP as well as a decrease in DBP in this elderly patient population (Table 1). Evaluation by tertiles of pulse pressure demonstrated an inverse association between pulse pressure and MAP, indicating that higher pulse pressure could not be attributed to an increase in distending pressure alone. A higher pulse pressure was associated with more advanced age, a higher proportion of women, greater frequency of previous use of antihypertensive medication, history of diabetes, baseline ECG abnormalities, and lower prevalence of alcohol use. There were minimal trends toward lower body mass index and decreased prevalence of current smokers in patients with higher pulse pressure. Among the female patients, higher pulse pressure was also associated with less frequent estrogen use.

Univariate analysis was used to assess the impact of a variety of baseline variables on stroke (n=262) and total mortality (n=455). The effects of pulse pressure and MAP on stroke, the primary end point of SHEP, were evaluated with a Cox proportional hazards model that adjusted for significant univariate predictors of stroke (Table 2). In this multivariate analysis, for each 10-mm Hg increase in pulse pressure, there was an 11% (95% confidence interval, 1% to 22%) increase in the risk of stroke (Table 2). Furthermore, for each 10-mm Hg increase in MAP, there was an independent 20% increase in the risk of stroke, confirming the additive prognostic effects of the mean and pulsatile components of blood pressure on the risk of stroke.

To determine whether pulse pressure and MAP provide independent prognostic information concerning the risk of death in this population, a Cox proportional hazards model was constructed that included these variables as well as variables that were significant predictors of all-cause mortality on univariate analysis. In this mortality analysis, pulse pressure was again independently predictive of total mortality (Table 2). For each 10-mm Hg increase in pulse pressure, there was a 16% (95% confidence interval, 8% to 24%) increase in the risk of death. MAP was also predictive of increased mortality. For each 10-mm Hg increase in

| TABLE 1. Baseline Characteristics by Pulse Pressure Tertile |
|----------------------------------|----------------|----------------|----------------|-----|
| Factor                          | First (n=1494) | Second (n=1634) | Third (n=1608) | P   |
| Pulse pressure range, mm Hg     | 71–86          | 87–96           | >96            |     |
| SBP, mm Hg                      | 164±3          | 168±6           | 178±11         | <0.001 |
| DBP, mm Hg                      | 83±4           | 77±6            | 70±12          | <0.001 |
| MAP, mm Hg                      | 110±3          | 107±6           | 106±10         | <0.001 |
| Age, y                          | 69±6           | 71±6            | 74±7           | <0.001 |
| Race, % white                   | 85             | 88              | 86             | 0.096 |
| Gender, % men                   | 53             | 43              | 34             | <0.001 |
| Prior antihypertensive use, %    | 28             | 32              | 39             | <0.001 |
| Body mass index, kg/m²          | 27.8±4.9       | 27.5±5.1        | 27.3±5.1       | <0.012 |
| Current smoking, %              | 13             | 14              | 12             | <0.007 |
| History of diabetes, %          | 8              | 10              | 12             | <0.003 |
| Alcohol use (>1 drink/week), %  | 35             | 31              | 24             | <0.001 |
| ECG abnormality, %              | 58             | 59              | 66             | <0.001 |
| Estrogen use (women, n=2690), % | 8.7            | 9.2             | 5.4            | <0.002 |
Physiological Considerations

With aging and repetitive cyclical stress, there is a breakdown of the elastin in the walls of conduit vessels, which leads to reduced compliance of the vessel. This process appears to be accelerated by diseases such as diabetes and hypertension as well as by dietary factors, including high salt intake and menopause. Heart failure is also associated with increased conduit vessel stiffness, possibly because of the effect of neurohumoral activation. Stiffening results in increased aortic impedance and an increase in pulse wave velocity. The increase in impedance causes a larger pulsatile pressure wave for a given pulsatile flow. Increased pulse wave velocity causes premature return of the pulse wave reflection from the periphery. The reflected wave, therefore, arrives in the central aorta during systole rather than diastole, further increasing central SBP and pulse pressure. This late augmentation of SBP progressively reduces, and ultimately eliminates, the normal augmentation of the pressure waveform that occurs as the pressure wave travels from the central aorta to peripheral arteries, such as the brachial artery, where blood pressure is usually evaluated. Thus, the increase in pulse pressure in the brachial artery is indicative of, but systematically and substantially underestimated, the increase in central aortic pulse pressure with advancing age and increasing conduit vessel stiffness.
Increased central aortic pulse pressure may play an important role in the pathogenesis and manifestation of carotid and coronary atherosclerosis rather than simply serving as a marker of the presence of disease. Increased pulse pressure has been shown to promote the development of atherosclerosis in a primate model and may increase the likelihood of plaque rupture as a result of the fatiguing effects of pulsatile strain. Several studies have documented the independent association between pulse pressure and measures of carotid artery disease, including intima-media thickness and plaque area. Pulse pressure has also been related to small-vessel disease in the cerebral circulation in animal models. Furthermore, resolution of small-vessel remodeling in those studies was more closely related to changes in pulse pressure than to changes in MAP. Increased prevalence and severity of white matter lesions, which are thought to be related to small-vessel disease, was associated with increased pulse pressure in 1920 men and women 55 to 72 years of age who were evaluated by magnetic resonance imaging as part of the Atherosclerosis Risk in Communities (ARIC) study.

This is the first analysis to evaluate the direct effects of pulse pressure as a risk factor for a cerebrovascular accident. Prior reports from the Framingham Heart Study and more recently from the Copenhagen City Heart Study were consistent with a role of pulse pressure as a predictor of stroke. Both studies found that SBP was superior to DBP as a determinant of stroke risk; however, neither evaluated the quantitative effect of pulse pressure. Furthermore, the Framingham analysis established the connection between increased SBP and conduit vessel stiffness by assessing an oscillometric finger-pulse tracing. They found that an abnormal pulse waveform, indicative of premature arrival of the reflected wave, was associated with an increased prevalence of isolated systolic hypertension.

Additional studies have suggested the importance of pulse pressure as an independent prognostic indicator for other cardiovascular end points, including myocardial infarction and death. The effects of SBP, DBP, and pulse pressure were studied in the Hypertension Detection and Follow-up Program. In patients who were untreated at baseline, pulse pressure was a significant predictor of total mortality. In a multivariate analysis, Madhaven et al found that increased pulse pressure was an independent predictor of myocardial infarction in a 5-year follow-up study of hypertensive individuals. In a large sample of a general population, Darg et al and later Benetos et al in a follow-up analysis, found that increased pulse pressure was associated with adverse cardiovascular events, independent of MAP and other cardiac risk factors.

The relationship between pulse pressure and adverse events was evaluated in the Survival and Ventricular Enlargement trial. Patients entered in the trial had recently had a myocardial infarction and a left ventricular ejection fraction ≤0.40. Despite the reduction in ejection fraction, pulse pressure emerged as a strong independent predictor of both total mortality and recurrent myocardial infarction in multivariate analyses that adjusted for a number of potentially confounding covariates. We recently studied the prognostic importance of pulse pressure in patients with left ventricular dysfunction entered in the SOLVD trial. In this population with left ventricular dysfunction and heart failure, pulse pressure was again associated with increased mortality. In contrast, in this heart failure–left ventricular dysfunction population, MAP was inversely correlated with increased risk of death, further emphasizing the independent nature of changes in MAP and pulse pressure and their effects on outcome.

The studies discussed have examined patients across a wide range of left ventricular function, from low in SOLVD to intermediate in SAVE to normal in SHEP. Together, they support the importance of aortic stiffening as an independent risk factor for adverse cardiovascular events. They raise the question of whether interventions that reduce conduit vessel stiffness will have improved efficacy with respect to cardiovascular end points. Also, they emphasize the need for a more direct measure of aortic stiffness, particularly if studies of the therapeutic effectiveness of reducing aortic stiffness are contemplated.

Clinical Implications
The observation that increased pulse pressure is associated with a higher risk of stroke and total mortality becomes particularly relevant as therapeutic options are shown to have a differential effect on conduit vessel stiffness. This differential effect may translate into improved efficacy with agents that preferentially reduce conduit vessel stiffness. Furthermore, such therapy may be preferentially targeted to patients with documented elevations of pulse pressure or conduit vessel stiffness. There is evidence that currently available therapeutic interventions may be able to modify conduit vessel stiffness. Lifestyle interventions, such as lower sodium intake and increased exercise, are associated with improved aortic compliance. Converting enzyme inhibitors have a highly favorable effect on conduit vessels. Low-dose diuretics effectively reduce conduit vessel stiffness and pulse pressure in elderly patients. In contrast, β-blockers, as monotherapy, have been shown to increase conduit vessel stiffness and the magnitude of the reflected wave. Results with calcium channel blockers have been mixed. Additional long-term studies with direct, repeated measurements of conduit vessel stiffness are needed to further refine the role of therapy targeted to reducing conduit vessel stiffness.

Another important clinical implication is that by use of only SBP or DBP for study inclusion criteria and therapeutic decisions, trialists and clinicians may be underestimating risk in patients with moderately increased SBP and reduced DBP.

Limitations
Pulse pressure is an imperfect measure of vascular compliance. It seems unlikely, however, that other potential determinants of increased pulse pressure, such as increased peak ejection rate or stroke volume, would be associated with an adverse prognosis. Nonetheless, it is clear that more direct measures of conduit vessel stiffness would be...
useful in future studies. This analysis was exploratory in nature, because an analysis of the association of pulse pressure with adverse events (stroke and death) was not a prespecified end point of SHEP. The findings of this analysis apply to elderly patients with isolated systolic hypertension, specifically the population randomized into SHEP. However, the prognostic importance of pulse pressure on total mortality has now been demonstrated across a wide range of patient populations.

Conclusions
This study provides strong evidence of an association of increased conduit vessel stiffness, as indicated by increased pulse pressure, with stroke and total mortality in elderly patients with isolated systolic hypertension. More study is needed to determine whether therapeutic interventions that preferentially alter conduit vessel stiffness can more favorably alter stroke and mortality rates.

References
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