

Determinants and Prognostic Information Provided by Pulse Pressure in Patients With Coronary Artery Disease Undergoing Revascularization (The Balloon Angioplasty Revascularization Investigation [BARI])

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Arterial stiffness, as evidenced by increased pulse pressure (PP), is associated with adverse cardiovascular events. However, the prognostic importance of PP in patients who have undergone revascularization is unknown. We examined the prognostic importance of PP and predictors of increased PP in patients entered into the Balloon Angioplasty Revascularization Investigation (BARI). Estimated correlation and standardized regression coefficients were reported, indicating the relative magnitude of independent effects of baseline characteristics on PP. The independent association of PP and outcome over 5 years was determined. Baseline characteristics independently associated with PP were higher mean arterial pressure, older age, female sex, noncoronary vascular disease, history of diabetes mellitus, and history of hypertension ($p < 0.001$ for all). Cox regression covariates significantly associated with time to death were age, smoking, male gender, diabetes history, congestive heart failure, and baseline use of an-

giotensin-converting enzyme inhibitors, diuretic, or digoxin. When PP was added to the model, it was found to be an independent predictor of time to death ($p = 0.008$). When PP and mean arterial pressure were added to the model, PP remained significantly associated with time to death ($p = 0.033$). When renal disease and noncoronary vascular disease were added to the model, the relative risk declined from 1.07 to 1.04 and the association was no longer statistically significant. Thus, increased PP is directly and independently associated with mean arterial pressure, hypertension, age ≥ 65 years, diabetes mellitus, and the presence of noncoronary vascular disease, and inversely associated with a history of myocardial infarction. After coronary revascularization, PP, reflecting arterial stiffness, is independently associated with total mortality. ©2001 by Excerpta Medica, Inc.

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There is a growing body of evidence linking increased arterial stiffness, as indicated by increased pulse pressure (PP), to stroke, myocardial infarction, and to cardiovascular and all-cause mortality.¹⁻⁵ The association of increased PP with adverse cardiovascular events has been found across the spectrum of left ventricular function, from markedly reduced to normal, and in a variety of disease states, including heart failure, coronary disease, and isolated systolic hypertension. However, an assessment of the prognostic importance of PP in a patient population undergoing

coronary revascularization has not been reported. The present study examines the prognostic significance of PP in patients with coronary artery disease who underwent revascularization and who were entered into the Bypass Angioplasty Revascularization Investigation (BARI).^{6,7} Patient characteristics that were associated with increased conduit vessel stiffening, as evidenced by elevated PP, were also studied.

METHODS

A detailed description of the BARI trial⁶ and its results⁷ have been reported previously. Briefly, BARI was a randomized trial comparing an initial strategy of percutaneous transluminal coronary angioplasty (PTCA) to an initial strategy of coronary artery bypass grafting (CABG) in patients with multivessel coronary disease and severe angina or ischemia. From August 1988 to August 1991, patients were randomized at 18 clinical centers in the United States and Canada. These patients were judged to be suitable candidates for either PTCA or CABG. Patients who underwent a previous revascularization procedure, who had single-vessel coronary disease, primary congenital, valvular,

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TABLE 1 Baseline Characteristics by Quartile of Pulse Pressure

	PP Quartiles				p Value
	1 (n = 945)	2 (n = 1,032)	3 (n = 936)	4 (n = 924)	
PP range (mm Hg)	0-41	42-50	50-62	63-132	
Systolic pressure (mm Hg)	112 ± 10	123 ± 11	134 ± 11	152 ± 16	<0.001
Diastolic pressure (mm Hg)	76 ± 9	76 ± 10	76 ± 11	76 ± 11	0.60
Mean arterial pressure (mm Hg)	88 ± 9	91 ± 10	95 ± 11	101 ± 12	<0.001
Age (yrs)	58 ± 10	60 ± 9	62 ± 9	66 ± 8	<0.001
Ejection fraction (%)	59 ± 12	60 ± 12	62 ± 13	64 ± 12	<0.001
Women		23%	29%	34%	<0.001
African-American	3%	6%	6%	5%	0.049
Treated diabetes mellitus	11%	16%	18%	27%	<0.001
Systemic hypertension	35%	41%	54%	67%	<0.001
Prior myocardial infarction	60%	55%	49%	44%	<0.001
Renal disease	1%	2%	1%	3%	0.015
Noncoronary vascular disease*	11%	12%	16%	23%	<0.001
Cigarette smoker	74%	71%	68%	64%	<0.001
Congestive heart failure (%)	6%	7%	7%	8%	0.16
Medicine Use					
β blocker	60%	54%	54%	49%	<0.001
Calcium antagonists	72%	74%	77%	78%	0.001
Aspirin	79%	77%	76%	73%	0.003
Digitalis & derivatives	6%	5%	9%	10%	<0.001
ACE inhibitors	9%	9%	10%	14%	<0.001
Diuretic	18%	19%	25%	28%	<0.001

*Lower extremity vascular surgery, intermittent claudication or aortic aneurysm, history of stroke, transient ischemic attack, carotid endarterectomy, or carotid disease documented by bruit or ultrasound.

Analysis of variance for continuous variable.

Mantel-Haenszel for categorical variable.

ACE = angiotensin-converting enzyme.

or nonischemic myocardial heart disease, or were <17 or >80 years old, were excluded. In addition, 2,010 patients who were otherwise eligible but did not consent to randomization were followed in a prospective registry. The analysis presented here includes all 3,837 patients from the randomized trial and the registry who had blood pressure data available and who underwent revascularization.

Follow-up contacts were made at 4 to 14 weeks, 6 months, and annually after initial revascularization. At the time of the analysis, patients had been followed for an average of 5.4 years. At each contact, information pertaining to vital status, myocardial infarction (MI), angina symptoms, and additional revascularization procedures was obtained. Ascertainment of vital status was 98% complete at the time the data in this study were assembled. Cause of death was determined by an independent morbidity and mortality review committee. Myocardial infarction was defined as new pathologic Q waves according to the Minnesota code^{8,9} or new left bundle branch block with abnormal cardiac enzyme levels. All electrocardiograms were interpreted by a central electrocardiographic and myocardial infarction classification laboratory at St. Louis University. All angiograms were evaluated by a central radiographic laboratory located at Stanford University. The University of Pittsburgh served as the coordinating center for the study and was responsible

for study administration, data management, and statistical analysis.

Blood pressure values were based upon a single cuff pressure taken at the baseline examination. PP was calculated as the difference between systolic and diastolic pressure as determined by standard sphygmomanometry at the time of screening. Mean arterial pressure was calculated as (systolic pressure + 2 diastolic pressure)/3.

Statistical analysis: Patients were categorized based on quartiles of PP and mean arterial pressure. Distribution of patients' demographic and clinical characteristics and medication use by quartiles of PP and mean arterial pressure were examined using a Wilcoxon test for continuous variables and a chi-square test for categorical variables. The correlation between baseline characteristics and PP was determined using a multivariate general linear model. Factors related to PP in univariate analysis ($p < 0.05$) were included in the multivariate model and a backward stepped approach was used. Estimated standardized regression coefficients were reported to indicate the magnitude of their independent and relative predictive effects on PP.

After verifying the proportional hazards assumption, Cox regression analysis was used to determine the association between PP and survival over 5 years independent of other risk factors. Registry patients who were treated medically were excluded. Risk ratios and their 95% confidence intervals are reported. The proportional hazards assumption was not met for PP. This indicates that the reported risk ratio for PP cannot be assumed to be constant over the 5-year period, but is an average risk over that period.

RESULTS

The 4 blood pressure variables (systolic blood pressure, diastolic blood pressure, mean arterial pressure, and PP) were not normally distributed (Kolmogorov test, $p < 0.01$ for all). Mean arterial pressure ranged from 63 to 143 mm Hg (mean 94; median 93). PP ranged from 20 to 132 mm Hg (mean 54; median 50). Diastolic pressures remained essentially constant across the quartiles of PP so that increasing PP in this cohort was predicated upon increasing systolic pressure.

PP was divided into quartiles and evaluated against a number of baseline factors (Table 1). Higher PPs were seen for older subjects, women, diabetics, and for patients with a history of hypertension, renal disease, or noncoronary vascular disease. Patients with a history of myocardial infarction tended to have a

TABLE 2 Independent Associations With Pulse Pressure

	Standardized Regression Coefficient	p Value
Mean arterial pressure	0.401	<0.001
Age \geq 65 yrs	0.215	<0.001
Treated diabetes mellitus	0.082	<0.001
Systemic hypertension	0.077	<0.001
Noncoronary vascular disease*	0.067	<0.001
Women	0.066	<0.001
History of myocardial infarction	-0.041	0.004

*Lower extremity vascular surgery, intermittent claudication or aortic aneurysm, history of stroke, transient ischemic attack, carotid endarterectomy, or carotid disease documented by bruit or ultrasound.

lower PP as did those with a history of smoking. PP was also associated with the use of a number of baseline medications. Subjects taking aspirin or β blockers tended to have lower PP, whereas those taking digitalis, angiotensin-converting enzyme inhibitors, or diuretics tended to have higher PPs. Ejection fraction was directly and significantly correlated with an increasing quartile of PP. PP was also found to be highly correlated with mean arterial pressure.

Independent positive associations were found between PP and mean arterial pressure, age, female sex, noncoronary vascular disease, history of diabetes, and a history of hypertension (Table 2, $p < 0.001$ for all). PP was inversely associated with a history of myocardial infarction (Table 2, $p = 0.004$). Smoking was not a significant correlate of PP in multivariate analysis.

In univariate analysis, quartile of PP was significantly associated with time to death (Figure 1). The effect was particularly strong for the highest quartile of PP. To determine whether this effect was independent of other factors associated with mortality, a Cox proportional hazards model was used. The model was first developed excluding the variables of renal disease or noncoronary vascular disease because these are concomitant disease conditions known to be associated with vascular stiffening.¹⁰ Important covariates significantly associated with time to death were age, smoking, male gender, history of diabetes, use of angiotensin-converting enzyme inhibitors, diuretic or digitalis use at baseline and congestive heart failure at baseline. When PP was added to the model, it was found to be a significant independent predictor of time to death ($p = 0.008$). However, when mean arterial pressure was used in place of PP, it was found not to be significantly associated with time to death ($p = 0.107$). When PP and mean arterial pressure were added to the model, PP remained significantly associated with time to death ($p = 0.033$). When renal disease and noncoronary vascular disease were added to the model, the relative risk declined from 1.07 to 1.04 and the association was no longer statistically significant.

When cardiac death was used as the end point, neither PP nor mean arterial pressure were found to be significantly predictive. Likewise, when evaluating the end points of angina, exercise-induced angina and

repeat revascularization, no significant contribution was made by either PP or mean arterial pressure.

DISCUSSION

Pulse pressure and clinical events: This study is the first to examine the prognostic importance of PP in a population of coronary patients who underwent revascularization. The analysis demonstrates that PP, but not mean arterial pressure, is independently associated with mortality in the BARI patients. The loss of significance with the addition of noncoronary vascular disease reflects the fact that the PP (and thus, arterial stiffness) is due to abnormality of the peripheral vasculature. Further, the association of renal dysfunction and increased arterial stiffness has been shown previously.¹⁰

Comparison with prior studies relating pulse pressure to clinical events: These data, associating adverse outcomes with increased PP, are consistent with growing literature suggesting the prognostic importance of arterial stiffness. Domanski et al¹ investigated the association of PP and mortality in 6,781 patients with left ventricular ejection fraction ≤ 0.35 randomized into the Studies of Left Ventricular Dysfunction (SOLVD). In a multivariate analysis that adjusted for known covariates, including treatment assignment to enalapril or placebo, higher PP was an independent predictor of total and cardiovascular mortality (relative risk for total mortality 1.05 per 10 mm Hg increment; $p = 0.02$). Interestingly, in the SOLVD database, mean arterial pressure was inversely related to total and cardiovascular mortality.

Chae et al³ examined 1,621 men and women who had PP ascertained in the community-based East Boston Senior Health Project and who were followed for up to 3.8 years for the development of congestive heart failure. After controlling for known covariates, PP was found to be an independent predictor of development of congestive heart failure (relative risk 1.14 for each 10 mm Hg increase in PP; $p < 0.01$).

Mitchell et al⁵ studied PP as a predictor of mortality in 2,231 patients 3 to 16 days after a myocardial infarction who were enrolled in the Survival and Ventricular Enlargement (SAVE) trial. In a multivariate analysis, PP remained a significant predictor of total mortality (relative risk 1.08 per 10 mm Hg increment in PP; $p < 0.05$) as well as recurrent myocardial infarction.

Domanski et al² studied 4,736 patients with isolated systolic hypertension entered into the Systolic Hypertension in the Elderly Program (SHEP) to determine the relation of PP to prognosis. The data from this study demonstrated a significant 16% increase in risk of all-cause mortality and a significant 11% increase in stroke risk for each 10 mm Hg increment in PP.

These studies (SOLVD, SHEP, SAVE, and East Boston) demonstrate the prognostic importance of PP across the spectrum of left ventricular dysfunction, from markedly depressed in SOLVD to moderately depressed in SAVE to normal in SHEP and East Boston.

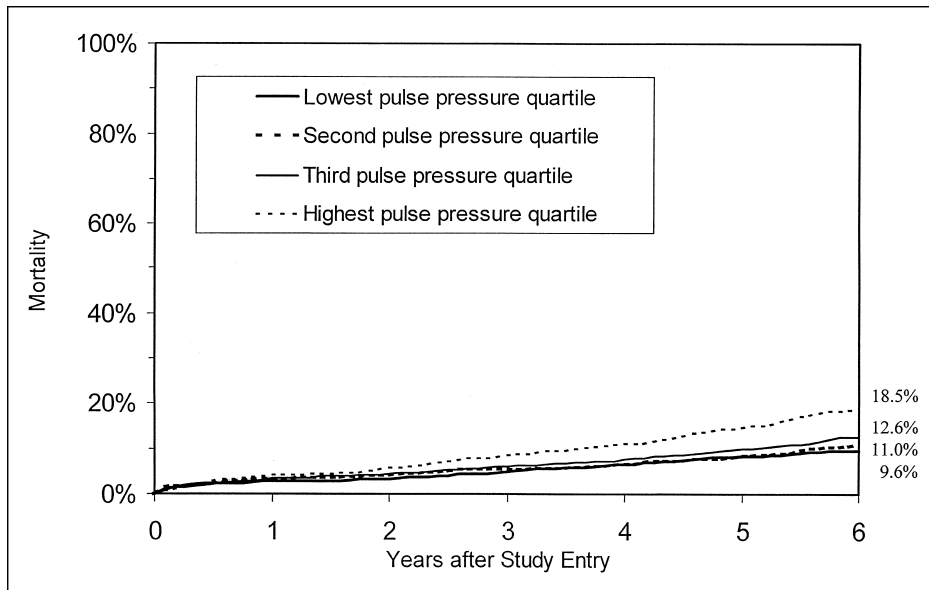


FIGURE 1. Kaplan-Meier estimates: mortality for each pulse pressure quartile.

TABLE 3 Independent Predictors of Total Mortality*

	Relative Risk	95% Confidence Limits	p Value
PP 10 mm Hg increment	1.08	1.01–1.15	0.027
Mean arterial pressure 10 mm Hg increment	1.02	0.93–1.11	0.75
Treated diabetes	1.78	1.29–2.47	<0.001
Age ≥65 yrs	1.71	1.39–2.11	<0.001
Ever smoked	1.49	1.19–1.87	<0.001
ACE inhibitor	1.61	1.25–2.09	<0.001
Diuretics	1.76	1.40–2.21	<0.001
Digitalis	1.69	1.26–2.26	<0.001
Congestive heart failure	1.55	1.14–2.10	0.005

*Model also controls for study group (randomized vs registry), revascularization (PTCA vs CABG), gender, and diabetes by revascularization interaction term.
Abbreviation as in Table 1.

The effect of aging on stiffness is likely independent of the progression of atherosclerosis. In a study of changing arterial stiffness in 480 Chinese patients, there was an age-associated increase in arterial stiffness in a population known to have a low risk of atherosclerosis and in whom there was no peripheral arterial disease.¹¹ As discussed previously, these data underscore the possible etiologic significance of increased arterial stiffness in the development of atherosclerosis. Arteriosclerotic changes are accelerated by the damaging effects of hypertension, another independent correlate of increased PP in our study. In SAVE, hypertension was also an important correlate of increased PP.⁵

Noncoronary vascular disease was independently associated with increased PP. The presence of atherosclerosis is not confined to a single region of the vascular system and it would be expected that there would be atherosclerosis and stiffening throughout the vascular tree when it is found in one region. This

means that the presence of noncoronary vascular disease would make the presence of coronary disease (as a basis for cardiovascular death) likely.

Our finding of higher PP in women is consistent with a number of observations in the middle aged and elderly population.^{1,2,4} Women have a lower PP from menarche to menopause. Starting at approximately age 55 years, there is a substantial increase in the slope of the relation between PP and age in women. As a result, the average PP in women reaches or exceeds that in men by the finish of the sixth decade.^{12–17} The rapid increase in PP just after the menopause is likely the direct result of estrogen withdrawal and corresponds to the concurrent dramatic increase in the prevalence of cardiovascular disease after menopause.¹⁷

The association of myocardial infarction with reduced PP is likely related to a reduction of left ventricular function in these patients and a resulting reduction in the stroke volume generated.

Study limitations: PP depends on stroke volume and peak aortic flow. For this reason, it could be reduced after extensive myocardial infarction obscuring the relation between PP and clinical end points. Nonetheless, a significant relation between PP and adverse clinical events was found in this study.

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