

# Pulse Pressure and Long-Term Survival After Coronary Artery Bypass Graft Surgery

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**BACKGROUND:** Data from longitudinal studies reveal that widened pulse pressure (PP) is a major predictor of coronary heart disease and mortality, but it is unknown whether PP similarly decreases survival after coronary artery bypass graft (CABG) surgery for coronary heart disease. We therefore assessed long-term survival in patients with increased PP at the time of presentation for CABG surgery.

**METHODS:** In this retrospective observational study of patients undergoing CABG surgery between January 1993 and July 2004, 973 subjects were included for assessment of long-term survival. Baseline arterial blood pressure (BP) measurements were defined as the median of the first 3 measurements recorded by the automated record keeping system before induction of anesthesia. The effect of baseline PP on survival after surgery was evaluated using a Cox proportional hazards regression model and bootstrap resampling with baseline mean arterial BP, systolic BP, diastolic BP, diabetes, Hannan risk index, aprotinin use, and cardiopulmonary bypass time as covariates.

**RESULTS:** There were 220 deaths (22.9%) during the follow-up period (median, 7.3 yr [Q1: 5, Q3: 10 yr]) including 94 deaths from cardiovascular causes. Increased baseline PP was a significant predictor of reduced long-term survival ( $P < 0.001$ ) along with Hannan risk index ( $P < 0.001$ ), duration of cardiopulmonary bypass ( $P < 0.001$ ), and diabetes ( $P < 0.001$ ). Baseline systolic ( $P = 0.40$ ), diastolic ( $P = 0.38$ ), and mean arterial BPs ( $P = 0.78$ ) were not associated with long-term survival. The hazard ratio for PP (adjusted for other covariates in the model) was 1.11 (1.05–1.18) per 10-mm Hg increase.

**CONCLUSIONS:** An increase in perioperative PP is associated with poor long-term survival after CABG surgery. Together with our previous report linking PP to in-hospital fatal and nonfatal vascular complications, the established models for surgical risk assessment, patient counseling, and treatment should be revised to include PP.

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Increased arterial blood pressure (BP) is a well-known risk factor for cardiovascular morbidity and mortality. Although peak systolic BP (SBP) and end-diastolic BP (DBP) have frequently been used to define this risk, it has been suggested that pulse pressure (PP, the difference between SBP and DBP) may be a more powerful predictor of cardiovascular events. For example, in patients with impaired left ventricular function, PP measured at the brachial artery is an

independent predictor of myocardial infarction (MI).<sup>1</sup> Similarly, in subjects 65 yr or older, a 10-mm Hg increment in PP was associated with a 12% increase in coronary heart disease risk, a 14% increase in congestive heart failure risk, and a 6% increase in overall mortality.<sup>2</sup>

Recent data have highlighted the importance of PP over other standard BP measures for identifying risk for adverse perioperative outcomes in the perioperative period. From an observational database of 5436 patients undergoing coronary artery bypass graft (CABG) surgery enrolled at 70 centers in 60 countries, we demonstrated that a 20-mm Hg increment in PP increased the odds of developing renal dysfunction by 50%.<sup>3</sup> An increase in PP was also associated with greater fatal and nonfatal adverse cerebral and cardiac outcomes before hospital discharge.<sup>4</sup> These and other data in normotensive and hypertensive populations indicate that aortic stiffness associated with aging and manifested by a widening PP may contribute significantly to long-term risk.<sup>5–9</sup> We therefore hypothesized that an increase in PP at the time of presentation for CABG surgery is associated with decreased long-term survival.

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## METHODS

### Patient Selection

The study was approved by the IRB of Duke University Medical Center (Durham, NC) as a retrospective data review. Detailed clinical data were collected from prospectively entered databases in all patients who underwent CABG surgery between January 1993 and July 2004, and who were enrolled in studies (observational or placebo arm only) evaluating cognitive decline after surgery. Patients were excluded from participation in these cognitive studies if they had symptomatic cerebrovascular disease (e.g., stroke with a residual deficit), psychiatric illness (any clinical diagnoses requiring therapy), renal failure (serum creatinine >2 mg/dL), active liver disease (liver function tests >1.5 times the upper limit of normal), alcoholism (>2 drinks/day), chronic anemia (hematocrit <30%), or were unable to read or had less than a seventh grade education. In addition, any patient with a perioperative intraaortic balloon pump or with more than mild aortic insufficiency on the intraoperative transesophageal echocardiographic examination was excluded from the current analyses.

### Data Sources and Collection

Clinical data were gathered from the Duke Databank for Cardiovascular Diseases, a large, quality-assured data repository for patients undergoing cardiovascular procedures at Duke University Medical Center that has been previously described.<sup>10</sup> Perioperative clinical data gathered included age, sex, perioperative ejection fraction, left main occlusion >90%, presence of congestive heart failure, unstable angina, diabetes, chronic obstructive pulmonary disease, dialysis dependence or MI within 7 days, and aortic cross-clamp time. These were used to calculate a modified score for each patient based on the index developed and validated by Hannan et al.<sup>11,12</sup> Follow-up was conducted by the Duke Clinical Research Institute Follow-up Services group, which is responsible for collecting annual follow-up mortality data and nonfatal end point information for the Duke Databank for Cardiovascular Diseases. The annual surveys collect data on general health, hospitalizations, MI, stroke, cardiac procedures, and medication use. Patients are surveyed 6 mo after an index visit and yearly thereafter with a mailed, self-administered survey with a phone-administered survey to nonresponders. Follow-up is 95% complete for mortality, and patients who are lost to follow-up (2%) or who have asked to be withdrawn (3%) are submitted for an annual search of the National Death Index. Death information is thus collected from next-of-kin interviews, hospital discharge summaries, death certificates, and cause of death provided from the National Death Index according to the International Classification of Diseases. Cause of death is assigned after agreement from independent reviews by a death committee.

### Assessment of BP

Intraoperative invasive BP was recorded every minute by an automated anesthesia record keeping system (Arkive™, Diatek, San Diego, CA and SATURN™, North American Draeger, Telford, PA). Baseline SBP, DBP, PP, and mean arterial BP (MAP) were defined as the median of the first 3 measurements recorded by the automated record keeping system before induction of anesthesia.

### Statistical Analysis

The primary outcome measure was defined as all-cause mortality during the follow-up period. An uncensored observation represented “complete data”: death had occurred and the time to death after CABG surgery was known. In contrast, the absence of any mortality during the follow-up period represented a censored observation. Freedom from mortality was assessed by constructing survival curves using the Kaplan–Meier method. Individual survival curves were compared using the log-rank test. We used Cox regression methods to remove variability in mortality that is accounted for by the Hannan index of in-hospital mortality.<sup>11,12</sup> The index includes most traditional risk variables for cardiac-related mortality, such as age, sex, hemodynamic state, ventricular function, extent of coronary disease, and preprocedural MI, and relevant comorbidities, including cerebrovascular disease, renal dysfunction, chronic obstructive pulmonary disease, and peripheral vascular disease. We chose to use this index, which was developed independently in different patients, to remove the risk of overfitting our data with a high-dimensional multivariable model using concurrent covariates. The relation between PP and risk of mortality was evaluated using a Cox proportional hazards regression model with baseline MAP, SBP, and DBP, diabetes, Hannan risk index, aprotinin use, and cardiopulmonary bypass time as covariates. For purposes of internal validation, we fit the multivariable models to 5000 bootstrap samples of the dataset. The 95% confidence intervals (CIs) for the hazard ratio (HR) of PP and the interaction between PP and Hannan risk index were obtained by bootstrap resampling. For each bootstrap sample, patient records were randomly sampled from the dataset with replacement, and a Cox proportional hazard model was fit to the sample. A point estimate of the HR was obtained for each bootstrap sample. A 95% CI for the HR for PP was computed from the 2.5 and 97.5 percentiles of the HR distribution resulting from 5000 bootstrap samples. Analyses were conducted using SAS (version 9.13; Cary, NC); a 2-tailed *P* value <0.05 was considered significant.

## RESULTS

Between January 1993 and July 2004, 973 patients were enrolled in 13 trials evaluating cognitive decline after CABG surgery. Twelve subjects were excluded because of invalid BP records and 1 was excluded

**Table 1.** Demographic Characteristics of the Study Population

Age, yr (SD)	62.3 (10.4)
Gender (% female)	27
Race (% Caucasian)	85.6
Weight in kg (SD)	86.5 (18.0)
Hypertension (%)	63.9
Diabetes (%)	31.0
Previous MI (%)	45.3
Congestive heart failure, NYHA $\geq 2$ (%)	14.7
Chronic obstructive pulmonary disease (%)	7.3
Peripheral vascular disease (%)	11.5
Prior cardiac surgery (%)	2.0
Off-pump CABG (%)	2.0
Intraoperative aprotinin use (%)	3.4
Ejection fraction (SD)	53 (12)
Number of grafts (SD)	3.1 (0.9)
Cross-clamp time, min (SD)	59 (23)
CPB time, min (SD)	109 (39)
Hannan risk index, median (Q1, Q3)	0.72 (0.44, 1.50)
Baseline systolic blood pressure, median (Q1, Q3)	145 (128, 165)
Baseline diastolic blood pressure, median (Q1, Q3)	66 (60, 74)
Baseline mean arterial blood pressure, median (Q1, Q3)	94 (84, 105)
Baseline pulse pressure, median (Q1, Q3)	78 (65, 95)

MI = myocardial infarction; NYHA = New York Heart Association; CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; Q1 = 25th percentile; Q3 = 75th percentile.

because of an indwelling intraaortic balloon pump. Demographic characteristics of the study population are presented in Table 1. Sixty-four percent of the subjects reported a history of hypertension. Baseline SBP and MAP were mildly increased in this cohort, whereas PP was moderately increased at a median of 78 mm Hg. In the 960 subjects who met inclusion criteria, the median follow-up time was 7.3 yr (Q1: 5, Q3: 10 yr).

There were 220 deaths (22.9%) during the follow-up period. Within the 220 mortality events, 94 were from cardiovascular causes, whereas 126 cases included other medical or unobserved deaths. Baseline PP was a significant predictor of long-term survival ( $P < 0.001$ ) along with Hannan risk index ( $P < 0.001$ ), duration of cardiopulmonary bypass ( $P < 0.001$ ), and diabetes ( $P < 0.001$ ) (Table 2, Fig. 1). Of note, baseline SBP ( $P = 0.40$ ), DBP ( $P = 0.38$ ), and MAP ( $P = 0.78$ ) did not show a significant independent effect in this model. There was also a significant ( $P = 0.007$ ) interaction of PP with Hannan risk, such that the effect of PP on survival was greater for lower Hannan risk than higher-risk patients (Fig. 2). Because of this interaction, a direct HR for PP cannot be easily interpreted. However, in a simpler model not considering the interaction, the HR for PP (adjusted for other covariates in the model) was 1.11 per 10-mm Hg increase (95% CI: 1.05–1.18).

Bootstrap estimates of a 95% CI for the HR yielded 1.04–1.12 for PP (per 10-mm Hg increase) in a model with main effects only. The bootstrap 95% CI for PP does not include 1, indicating that the significant effect

inferred for PP is robust to minor variations in the data. For the interaction between PP and Hannan risk index, the bootstrap 95% CI is wider and includes 1 (0.73–1.12), suggesting marginal robustness.

## DISCUSSION

Consistent with our previous studies demonstrating an association between baseline PP and short-term adverse renal, cardiac, and cerebral outcomes, we found in this observational study of 973 patients undergoing CABG surgery that an increase in PP is associated with long-term mortality. Importantly, pre-surgical SBP, DBP, and MAP, the more traditional measures of risk, were not predictive of long-term mortality.

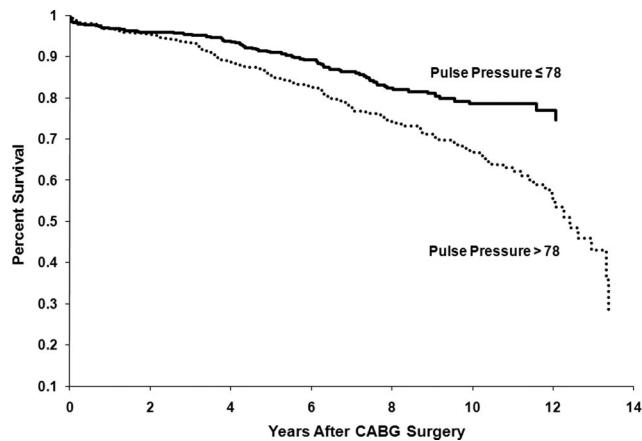
Over the last decade, increases in PP have been found to be associated with greater cardiovascular morbidity and mortality in community-dwelling adults.<sup>2,5,7,8,13,14</sup> For example, Franklin et al.<sup>7</sup> using the Framingham Heart Study demonstrated in a cohort of 1924 men and women followed over a 20-yr period that PP was superior to SBP and DBP in predicting coronary heart disease risk. Data from the Systolic Hypertension in the Elderly Program also demonstrated an 11% increase in stroke risk and a 16% increase in risk of all-cause mortality for each 10-mm Hg increase in PP, independent of the effects of MAP.<sup>8</sup> More recently, a study in 41,473 men and 28,516 women who underwent a standard health checkup between 1972 and 1988 and who were followed for a mean of  $15.3 \pm 4.7$  yr, revealed that PP was an independent risk factor for cardiovascular mortality, with a greater effect on coronary than stroke mortality.<sup>14</sup> When more specific measures of arterial stiffness such as the carotid-femoral pulse wave velocity are examined, similar associations are seen.<sup>15,16</sup> Laurent et al.<sup>15</sup> demonstrated in 1980 patients with essential hypertension that the odds ratios for all-cause and cardiovascular mortality for an increase in pulse wave velocity  $\geq 5$  m/s were 1.34 (1.04–1.74) and 1.51(1.08–2.11), respectively. We have previously shown that in patients undergoing cardiac surgery ( $n = 5436$ ), an increase in PP was independently associated with greater fatal and nonfatal adverse renal, cerebral, and cardiac outcomes before hospital discharge.<sup>3,4</sup> The current study confirms this risk beyond the immediate perioperative period by demonstrating decreased survival in the years after coronary revascularization in patients with an increase in PP.

The arterial tree fulfills 2 roles under normal conditions: a conduit role of delivering blood to peripheral tissues and a cushioning role that dampens the pressure oscillations from ventricular ejection such that capillary blood flow is near continuous.<sup>17–19</sup> Although the entire vascular tree participates in both of these functions, the aorta and its main branches have a dominant role in the cushioning function, whereas the distal arteries and arterioles are primarily

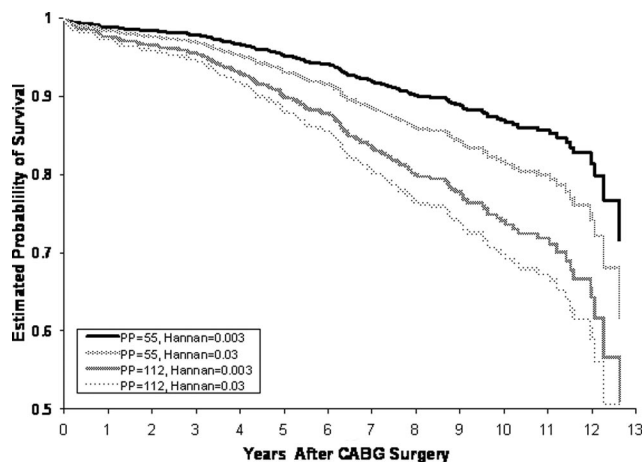
**Table 2.** Cox Proportional Hazards Regression Model for the Relationship Between Pulse Pressure and Mortality

Variable	df	Parameter estimate	Standard error	Hazard ratio (95% CI)	P
Baseline pulse pressure (per 10 mm Hg)	1	0.014	0.003	1.15 (1.07–1.23)	<0.001
Hannan risk index (per 0.01 unit)	1	20.84	4.90	1.23 (1.12–1.36)	<0.001
Baseline pulse pressure × Hannan risk index	1	−0.127	0.047	0.88 (0.81–0.97)	0.007
CPB time (per 10 min)	1	0.007	0.002	1.08 (1.04–1.12)	<0.001
Diabetes	1	0.550	0.156	1.73 (1.28–2.35)	<0.001
Intraoperative aprotinin use	1	0.769	0.408	2.16 (0.97–4.80)	0.059

CPB = cardiopulmonary bypass.



**Figure 1.** Unadjusted Kaplan–Meier point estimates for long-term survival after coronary artery bypass graft in subjects with baseline pulse pressure more than vs less than or equal to the median value (78 mm Hg).



**Figure 2.** Predicted survival probability for subjects with the 10th and 90th percentiles (chosen solely for illustrative purposes) of baseline pulse pressures and Hannan risk index demonstrating the interaction between the 2 such that a greater mortality effect of baseline pulse pressure is seen in subjects with lower Hannan risk.

involved in continuous blood flow distribution. When blood is ejected into the aorta, the incident pressure wave is reflected back at structural or functional points of discontinuity, occurring largely at the origins of arterioles.<sup>20</sup> Thus, the amplitude and shape of the arterial pressure wave represent a summation of the forward (incident) and reflected waves. In the young, the reflected waves return during diastole augmenting

diastolic myocardial perfusion. With aging, there is progressive arteriosclerosis and atherosclerosis leading to a diminution of the cushioning function, and therefore a reduced compliance. Increasing arterial stiffness causes central to peripheral pulse wave velocity (incident wave) to accelerate with early return of the reflected waves during late systole rather than diastole. Consequently, aortic systolic pressure (afterload) is augmented, whereas diastolic pressure is reduced (i.e., an increase in PP). The net effect of arterial stiffness includes an increase in left ventricular end-systolic afterload and stress, induction of left ventricular hypertrophy, increase in myocardial oxygen consumption, and impairment in ventricular ejection and diastolic function.<sup>13</sup>

Although increases in PP may have little effect on the microcirculation in most organs because the resistance offered by the small arteries and arterioles transforms the pulsatile flow to steady flow in the capillaries, the brain and kidney are not similarly protected because they have high resting flow (low resistance), and the pulsations may, therefore, extend further into the capillary system.<sup>19</sup> Brain and kidney arteries are thus subjected to higher pulsatile circumferential and longitudinal shear stress, and further increases in pulsatile stress as seen with PP hypertension can lead to endothelial, smooth muscle, and vascular disruption.<sup>17,21</sup> A widened PP can thus promote the development of atherosclerosis and increase the likelihood of plaque rupture and thrombosis.<sup>22–26</sup> PP has been associated not only with markers of arterial disease such as intima-media thickness and atherosclerotic plaque area<sup>27–29</sup> but also with impaired flow-mediated vasodilation<sup>30</sup> and higher levels of von Willebrand factor.<sup>31</sup> In our previous report, we demonstrated that the incidence of a cerebral event and/or death from neurologic complications nearly doubled for patients with PP >80 mm Hg vs ≤80 mm Hg (5.5% vs 2.8%;  $P = 0.004$ ).<sup>4</sup> Similarly, the odds of developing renal dysfunction and/or renal failure postoperatively were increased by 49% for every 20–mm Hg increase in PP above a threshold of 40 mm Hg.<sup>3</sup> Thus, the lower survival rate in our study population is likely a consequence of greater cardiac, cerebral, and renal complications in patients with a widened PP.

Currently, no specific treatment for widened PP is routinely implemented after cardiac surgery. Most

therapeutic strategies aim to aggressively reduce systolic hypertension, but such an approach can result in excessive lowering of DBP, which has been associated with increased mortality.<sup>32</sup> Antihypertensive drugs have been reported to have differential effects on SBP and DBP. For example, data from the REASON (Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study) study<sup>33</sup> demonstrate that for the same level of DBP reduction, very low dose combinations of an angiotensin-converting enzyme inhibitor (ACE-I) and a diuretic decreased SBP, and thus PP, to a greater degree than beta-blocker alone. This effect was not seen with ACE-I alone<sup>34</sup> and was much more pronounced in the central rather than the peripheral arteries.<sup>35</sup> Similarly, the Conduit Artery Function Evaluation study demonstrated in 2073 participants followed for 4 yr that an antihypertensive regimen consisting of ACE-I  $\pm$  calcium channel blockade decreased PP to a greater degree than treatment with a beta-blocker with or without a diuretic therapy.<sup>36</sup>

Limitations to our study include the fact that patients selected for this study were enrolled in trials assessing cognitive outcomes; as such, they were at lower risk for adverse cerebral and renal events. However, this limitation would only underestimate the relationship between PP and mortality because patients at higher risk for fatal cerebral and renal events were not included. A second limitation is the fact that PP is a less sensitive surrogate for arterial stiffness than other measures such as pulse wave velocity or measurement of central aortic augmentation pressure.<sup>8,18</sup> These measurements, however, are not routinely obtained in cardiac surgical patients. The use of the more sensitive measures of vascular stiffness would likely have strengthened the association between PP and mortality. Finally, this is an observational study and BP was managed according to routine clinical practice as opposed to a standardized regimen.

In conclusion, we demonstrate in this study that an increase in perioperative PP is associated with shorter long-term survival after CABG surgery. Importantly, presurgical SBP, DBP, and MAP, the more traditional measures of risk, were not predictive of long-term mortality. Together, these findings suggest that established models for surgical risk assessment and management of hypertension in the postsurgical patient should be reevaluated to include measurement and possibly treatment of high PP.

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