Preoperative B-type natriuretic peptide is as independent predictor of ventricular dysfunction and mortality after primary coronary artery bypass grafting

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Objective: Elevated B-type natriuretic peptide is associated with increased morbidity and mortality in ambulatory patients with congestive heart failure or acute coronary syndromes. Its utility in predicting adverse cardiac surgical outcomes is less certain. We hypothesized that preoperative plasma B-type natriuretic peptide would independently predict in-hospital postoperative ventricular dysfunction, hospital stay, and up to 5-year mortality after primary coronary artery bypass grafting.

Methods: This is a prospective, longitudinal study of 1023 patients at two institutions undergoing primary coronary artery bypass grafting with cardiopulmonary bypass. Ventricular dysfunction was defined as requirement for at least two inotropes or new intra-aortic balloon pump or ventricular assist device support after coronary artery bypass grafting. Multivariable analyses assessed independent roles of preoperative B-type natriuretic peptide in predicting postoperative ventricular dysfunction, hospital stay, and 5-year all-cause mortality.

Results: Preoperative plasma B-type natriuretic peptide concentration predicted ventricular dysfunction, hospital stay, and mortality in univariate and multivariable analyses. Logistic regression demonstrated preoperative B-type natriuretic peptide to independently predict ventricular dysfunction (odds ratio 1.92, 95% confidence interval 1.12–3.29, $P = .018$), after adjustment for preoperative left ventricular ejection fraction, congestive heart failure severity, and other clinical predictors. Multivariable Cox proportional hazards models showed preoperative B-type natriuretic peptide to independently predict hospital stay (hazard ratio 1.42, 95% confidence interval 1.18–1.72, $P = .0002$) and mortality (hazard ratio 1.89, 95% confidence interval 1.08–3.33, $P = .026$).

Conclusion: Preoperative plasma B-type natriuretic peptide independently predicted in-hospital ventricular dysfunction, hospital stay, and up to 5-year all-cause mortality after primary coronary artery bypass grafting.

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B-type natriuretic peptide (BNP) is secreted by cardiac ventricular myocytes in response to increased ventricular wall tension and promotes compensatory diuresis, natriuresis, and inhibition of the renin-angiotensin-aldosterone axis.¹ Elevated plasma BNP independently predicts intermediate to long-term morbidity and mortality in ambulatory patients with congestive heart failure (CHF)^{2–5} or acute coronary syndromes.^{6–9} For noncardiac surgical patients, elevated preoperative BNP independently predicts a composite of in-hospital adverse cardiac events, including cardiac death.¹⁰ Studies of the utility of preoperative plasma BNP for identifying risk in cardiac surgical patients have been inconsistent, probably because of limitations of small sample sizes or inclusion of diverse cardiac surgical procedures.^{11–15} We hypothesized that elevated preoperative BNP would independently predict the occurrence of in-hospital postoperative ventricular dysfunction and longer term all-cause mortality in patients undergoing primary coronary artery

Abbreviations and Acronyms

BNP	= B-type natriuretic peptide
CABG	= coronary artery bypass grafting
CHF	= congestive heart failure
CI	= confidence interval
CPB	= cardiopulmonary bypass
cTnI	= cardiac troponin I
IABP	= intra-aortic balloon pump
LVEF	= left ventricular ejection fraction
POD	= postoperative day
VAD	= ventricular assist device

bypass grafting (CABG) with cardiopulmonary bypass (CPB), even after adjustment for other established predictors of perioperative risk. We further hypothesized that incorporating preoperative plasma BNP data into established cardiac surgical mortality risk prediction models would significantly improve their ability to predict all-cause mortality up to 5 years after CABG.

Methods**Study Participants**

Patients aged 21 to 89 years undergoing primary CABG alone with CPB at Brigham and Women's Hospital, Boston, Mass, and Texas Heart Institute, St Luke's Episcopal Hospital, Houston, Tex, between August 2001 and June 2005 were enrolled consecutively into a prospective parent study (CABG Genomics Research Study, <http://clinicaltrials.gov/show/NCT00281164>)¹⁶ with the overall aim of identifying relationships among genotypic variation, biomarkers, and adverse perioperative outcomes. Institutional review board approval was obtained, and written informed consent was obtained from each patient before enrollment. Exclusion criteria included a preoperative hematocrit less than 25% or administration of leukocyte-rich blood products within 30 days before surgery. Patients undergoing emergency surgery; patients requiring preoperative inotropes, a preoperative intra-aortic balloon pump (IABP), or a ventricular assist device (VAD); and patients missing preoperative BNP data were prospectively excluded from analysis. Patients with severe renal dysfunction (preoperative hemodialysis or serum creatinine >3 mg/dL) were also excluded from analysis because of concern that perioperative dialysis would variably affect perioperative plasma BNP concentrations.^{17,18}

Data and Blood Collection

Data were collected for each enrolled patient during primary hospitalization with a study-specific case report form that included patient demographic information, perioperative risk factors, medications, perioperative medical and surgical parameters, and postoperative outcomes. To verify accuracy of records, computerized range and logic checking were automatically performed on all records, as was a manual audit of a proportion of records. Postoperative patient survival was assessed annually by mail and telephone questionnaires and by examination of the Social Security mortality index.

Plasma and serum samples obtained preoperatively and on postoperative days (PODs) 1 through 5 were stored in vapor-phase liquid nitrogen at -70°C until analysis. Preoperative (day of surgery) plasma BNP and cardiac troponin I (cTnI) and postoperative plasma BNP concentrations (PODs 1, 3, and 5) were measured at the Brigham and Women's Hospital Clinical Laboratory with ADVIA Centaur BNP and cTnI immunoassays (Siemens Medical Solutions Diagnostics, Tarrytown, NY). Timing choices for postoperative BNP measures were based on the occurrence of peak postoperative plasma BNP concentrations obtained from a pilot study of 116 CABG Genomics Research Study patients (data not shown).

Definitions

Postoperative ventricular dysfunction was defined as new requirement for at least 2 inotropes or the need for IABP or VAD insertion either intraoperatively after separation from CPB or postoperatively in the intensive care unit. Intraoperative and postoperative inotropic support was defined as continuous infusion of amrinone, dobutamine, dopamine ($>5 \mu\text{g}/[\text{kg} \cdot \text{min}]$), epinephrine, isoproterenol, milrinone, norepinephrine, or vasopressin. A dyspnea score was derived from the New York Heart Association classification, with a score of 1 indicating no dyspnea, a score of 2 indicating mild impairment of daily functioning, a score of 3 indicating substantial functional impairment when not at rest, and a score of 4 indicating functional impairment at rest.¹⁹ Urgent CABG was defined as surgery occurring within the same hospitalization as the diagnosis of an acute coronary event or coronary artery disease. Stenosis greater than 50% of the left anterior descending, left circumflex, or right coronary artery or of their major branches were quantified according to cardiac catheterization data and scored as regions of coronary arterial disease (1, 2, or 3 regions total). Stenosis greater than 50% of the left main coronary artery was counted as 2 regions of significant disease. Hospital stay included date of surgery and date of discharge as complete days of stay, with a 30-day postoperative follow-up period for this outcome. Extended hospital stay was defined as longer than 12 days (90th percentile) after surgery. Mortality was defined as death from any cause during the 5-year follow-up period after surgery.

Statistical Analysis

Statistical analyses were performed with SAS (version 9.1; SAS Institute, Inc, Cary, NC). On the basis of data from a previously conducted pilot study ($n = 116$), required sample size was estimated for greater than 99% power and a type I error of .05. This stringent power requirement was chosen to allow adequate sample size for assessment of preoperative BNP concentration as an independent predictor of postoperative ventricular dysfunction after adjustment for multiple covariates. Accordingly, at least 100 patients with ventricular dysfunction were needed to detect significant differences in baseline BNP concentrations.

Preoperative plasma BNP data were $\log_{10}$ transformed to a normal distribution before analysis. To examine the effects of preoperative BNP concentrations and other perioperative covariates on ventricular dysfunction, hospital stay, and 5-year postoperative mortality, χ^2 or Fisher exact tests were used for categorical covariates and Wilcoxon–Mann–Whitney rank sum tests were used for continuous covariates. Mantel–Haenszel χ^2 tests were used for ordinal variables. Paired comparisons were made when appropriate. Log-rank

tests were used to evaluate univariate associations between perioperative covariates and postoperative survival. To assess the relationship between preoperative BNP and other perioperative covariates with regard to in-hospital ventricular dysfunction, hospital stay, and 5-year mortality, covariates with a 2-tailed nominal P value less than .15 in univariate analyses and additional demographic variables were entered into a stepwise multivariable logistic regression for analysis of ventricular dysfunction and into Cox proportional hazards models for analysis of hospital stay and 5-year postoperative mortality. In the hospital stay analysis, patients who died within 30 days of surgery were counted as having a hospital stay of 30 days. Because plasma BNP concentration has been shown to increase with age,²⁰ female sex,²⁰ renal dysfunction,¹⁸ and reduced left ventricular ejection fraction (LVEF) and to decrease with obesity,²¹ these covariates were adjusted for in all multivariable analyses. Receiver operating characteristic curves were used to assess the relationship of preoperative BNP concentrations to postoperative ventricular dysfunction and mortality. Kaplan–Meier survival curves were constructed as appropriate, with Wilcoxon rank tests used to assess significant differences between stratified curves.

To assess the value of adding preoperative BNP concentration to established risk stratification models for predicting mortality after CABG, risk scores for each patient were calculated with the Cleveland Clinic,²² EuroSCORE additive²³ and logistic,²⁴ modified Parsonnet,²⁵ and New York State (www.health.state.ny.us/nysdoh/consumer/heart/1996-98cabg.pdf) models. Of 19 well-known cardiac surgical risk scoring systems, these five risk scores have been shown to be best in predicting 1-year mortality after CABG.²⁶ We used three statistical approaches (Nagelkerke generalized r^2 ,²⁷ the likelihood ratio test, and Akaike information criterion²⁸) to assess the benefit of adding preoperative BNP data to the five mortality risk scores to predict 5-year postoperative mortality. We also used these three statistical approaches to assess the abilities of the multivariable models developed in this study to predict postoperative ventricular dysfunction, hospital stay, and mortality with and without inclusion of preoperative BNP. F tests were used to compare generalized r^2 , and the likelihood ratio test statistic had an asymptotic χ^2 distribution.

Results

Of 1162 patients enrolled in the parent study, 139 were excluded from analysis for one or more of the following prospectively determined exclusion criteria: emergency surgery ($n = 4$); previous CABG ($n = 1$); valve ($n = 2$); or other cardiac ($n = 15$) surgery; off-pump surgery ($n = 39$); preoperative hemodialysis ($n = 1$) or preoperative serum creatinine level greater than 3 mg/dL ($n = 4$); preoperative inotropes ($n = 4$); preoperative IABP ($n = 27$) or VAD use ($n = 1$); concurrent cardiac valve surgery ($n = 50$); and missing preoperative BNP concentration ($n = 12$).

Patient Characteristics

Perioperative patient characteristics for the 1023 patients included in the study analysis are shown in Table 1 and are stratified by occurrence of postoperative ventricular dysfunction. Table 2 shows the type of ventricular support required by the patients with ventricular dysfunction. Patients with

postoperative ventricular dysfunction were significantly more likely to have higher preoperative BNP concentrations, as well as preoperative renal insufficiency; recent myocardial infarction according to patient history; preoperative cTnI level greater than 0.1 $\mu\text{g/L}$; reduced LVEF; higher dyspnea score; higher pack-year smoking history; preoperative angiotensin-converting enzyme inhibitor, diuretic, and digoxin use; and longer CPB and aortic crossclamp times (Table 1).

Relationship of Ventricular Dysfunction to Hospital Stay and Postoperative Survival

Patients with postoperative ventricular dysfunction had a significantly higher incidence of extended hospital stay (odds ratio 6.16, 95% confidence interval [CI] 3.88–9.77, $P < .0001$) than patients without postoperative ventricular dysfunction. During the 5-year postoperative follow-up period, 72 patients (7.0%) died, with mean time between surgery and death being 1.8 ± 1.4 years (range 0–5 years). Because only 10 patients died within 30 days after surgery, we did not assess predictors of short-term postoperative mortality. Mean follow-up for the 951 living patients was 3.6 ± 1.0 years (range 1.7–5 years), with 31.0% and 11.5% of patients having reached the 4- and 5-year follow-up points, respectively. Patients with postoperative ventricular dysfunction had significantly lower survival during the 5-year follow-up period (odds ratio 3.58, 95% CI 2.07–6.21, $P < .0001$) than did patients without postoperative ventricular dysfunction (Figure 1).

Relationship of Preoperative BNP to Postoperative Ventricular Dysfunction and Hospital Stay

Patients with ventricular dysfunction had significantly higher BNP concentrations at all perioperative time points relative to patients without ventricular dysfunction (Figure 2). Patients without postoperative ventricular dysfunction had BNP concentrations that peaked on POD 3 and then declined significantly, whereas patients with postoperative ventricular dysfunction had BNP concentrations that remained elevated throughout the observed postoperative period, without significant differences between PODs 3 and 5.

The value of preoperative BNP concentration for predicting postoperative ventricular dysfunction was evaluated after adjustment for the demographic characteristics of age, sex, and ethnicity; body mass index; institution; and other likely clinical predictors of postoperative ventricular dysfunction, including preoperative angiotensin-converting enzyme inhibitor use, heart failure score, renal insufficiency, and the other predictors listed in Table 3. Preoperative BNP concentration independently predicted postoperative ventricular dysfunction (odds ratio 1.92, 95% CI 1.12–3.29, $P = .018$). Addition of preoperative BNP to the multivariable model for predicting postoperative ventricular dysfunction (Table 3) significantly improved the model's predictive ability, as indicated by significant changes in the generalized r^2 ($P = .0004$)

TABLE 1. Patient characteristics stratified by ventricular dysfunction after primary coronary artery bypass grafting

	No dysfunction (n = 904)	Dysfunction (n = 119)	P value
Preoperative characteristics			
Age (y, mean $\pm$ SD)	63.7 $\pm$ 10.2	63.8 $\pm$ 10.6	.75
Female	169 (18.7%)	20 (16.8%)	.62
White	771 (85.3%)	102 (85.7%)	.90
Institution			.38
Brigham and Women's Hospital	665 (73.6%)	92 (77.3%)	
Texas Heart Institute	239 (26.4%)	27 (22.7%)	
Diabetes mellitus (n = 1022)	243 (26.9%)	41 (34.5%)	.08
Hypertension (n = 1020)	681 (75.6%)	92 (77.3%)	.68
Hypercholesterolemia (n = 1019)	682 (75.6%)	93 (79.5%)	.36
Obesity (body mass index >30 kg/m ²)	347 (38.4%)	49 (41.2%)	.56
Current smoker (n = 1017)	114 (12.7%)	10 (8.5%)	.19
Smoking (>30 pack-year history, n = 972)	231 (26.7%)	41 (38.7%)	.009
Renal insufficiency (creatinine 1.6–3.0 mg/dL, n = 1022)	44 (4.9%)	13 (10.9%)	.007
Myocardial infarction ≤ 2 wk preoperatively (n = 1022)	137 (15.2%)	40 (33.6%)	$<.0001$
Left ventricular ejection fraction (%), mean $\pm$ SD, n = 973)	53.7 $\pm$ 11.5	43.1 $\pm$ 15.8	$<.0001$
Dyspnea score (per New York Heart Association classification, n = 928)			.02
None or mild	435 (52.9%)	48 (45.3%)	
Moderate	301 (36.6%)	38 (35.9%)	
Severe	86 (10.5%)	20 (18.9%)	
Coronary artery regions with $>50\%$ stenosis (n = 1008)			.14
0–1	50 (5.6%)	3 (2.5%)	
2	141 (15.9%)	17 (14.3%)	
3	698 (78.6%)	99 (83.2%)	
Mitral insufficiency, moderate or severe (n = 975)	16 (1.9)	5 (4.4)	.09
Past arrhythmia (n = 1022)	79 (8.8%)	12 (10.1%)	.63
Preoperative B-type natriuretic peptide (pg/mL, median, 10th–90th percentile)	56.6 (11.2–250.7)	132.1 (19.0–696.9)	$<.0001$
Preoperative cardiac troponin I >0.1 μ g/L (n = 982)	238 (27.4%)	55 (48.7%)	$<.0001$
Preoperative medications			
Angiotensin-converting enzyme inhibitor (n = 1022)	397 (44.0%)	71 (59.7%)	.001
Diuretic (n = 1022)	165 (18.3%)	40 (33.6%)	$<.0001$
Statin	686 (75.9%)	90 (75.6%)	.95
Digoxin (n = 1022)	23 (2.6%)	8 (6.7%)	.01
β -Blocker	679 (75.1%)	96 (80.7%)	.18
Aspirin	674 (74.6%)	91 (76.5%)	.65
Nonaspirin platelet inhibitor (n = 1022)	176 (19.5%)	25 (21.0%)	.70
Intravenous heparin (n = 1022)	205 (22.7%)	37 (31.1%)	.04
Intravenous nitrate (n = 1020)	104 (11.5%)	16 (13.5%)	.54
Intraoperative characteristics			
Urgent surgery (n = 1021)	470 (52.1%)	68 (57.1%)	.30
Cardiopulmonary bypass time (min, mean $\pm$ SD)	93.3 $\pm$ 37.0	107.9 $\pm$ 33.3	$<.0001$
Aortic crossclamp time (min, mean $\pm$ SD, n = 1007)	68.4 $\pm$ 32.0	76.1 $\pm$ 29.5	.004
No. of coronary grafts (n = 1022)			.14
1–2	146 (16.2%)	11 (9.2%)	
3	398 (44.1%)	57 (47.9%)	
≥ 4	359 (39.8%)	51 (42.9%)	

Data are number and percentage of patients except as indicated.

and the likelihood ratio statistic ($P = .016$). The 75th (141 pg/mL) and the 90th (292 pg/mL) percentiles of preoperative BNP concentrations had high specificity but lower sensitivity for predicting postoperative ventricular dysfunction, as shown in Figure 3.

Because ventricular dysfunction is significantly associated with both extended hospital stay and 5-year postoperative mortality, we also assessed the value of preoperative BNP concentration for predicting postoperative hospital stay. Elevated preoperative BNP significantly increased

TABLE 2. Type of ventricular support required by 119 patients with ventricular dysfunction after primary coronary artery bypass grafting

Type of ventricular support	Patients with dysfunction	
	Intraoperative	Postoperative
2 Inotropes	57 (47.9%)	46 (38.7%)
≥3 Inotropes	9 (7.6%)	24 (20.2%)
Intra-aortic balloon pump insertion time	19 (16.0%)	12 (10.1%)
Ventricular assist device insertion time	0 (0%)	1 (0.8%)
Inotrope		
Amrinone	2 (1.7%)	2 (1.7%)
Milrinone	14 (11.8%)	19 (16.0%)
Dobutamine	6 (5.0%)	6 (5.0%)
Isoproterenol	1 (0.8%)	2 (1.7%)
Dopamine (>5 μg/[kg · min])	19 (16.0%)	16 (13.4%)
Epinephrine	87 (73.1%)	75 (63.0%)
Norepinephrine	39 (32.8%)	42 (35.3%)
Vasopressin	9 (7.6%)	40 (33.6%)

Data are number and percentage of patients with ventricular dysfunction.

the likelihood of longer hospital stay (hazard ratio 1.42, 95% CI 1.18–1.72, $P = .0002$) after adjustment for demographic characteristics, institution, CPB time, and preoperative variables including medications, LVEF, cTnI, renal insufficiency, heart failure score, pack-year smoking history, and number of diseased coronaries. Addition of preoperative BNP to the multivariable model for predicting postoperative hospital stay significantly improved the model's predictive ability, as indicated by significant changes in the generalized r^2 ($P = .0002$) and the likelihood ratio statistic ($P = .0002$).

Figure 1. Kaplan-Meier survival curves for all patients to 5 years after primary coronary artery bypass grafting according to presence or absence of postoperative ventricular dysfunction (VnD). Vertical bars indicate 95% confidence intervals for survival estimates for each year of postoperative follow-up.

Figure 2. Perioperative plasma B-type natriuretic peptide (BNP) concentrations for all patients stratified according to presence or absence of postoperative in-hospital ventricular dysfunction (VnD), with 10th, 25th, 50th, 75th, and 90th percentile values shown for each subgroup at each time point. Asterisk signifies $P < .0001$ for ventricular dysfunction versus no ventricular dysfunction; dagger signifies $P < .0001$ versus preoperative baseline; double dagger signifies $P < .0001$ versus previous postoperative day; section mark signifies $P = .02$ versus previous postoperative day.

Relationship of Preoperative BNP to Postoperative Survival

The preoperative BNP concentrations of patients who died during the 5-year postoperative follow-up period (median 111 pg/mL, 10th–90th percentile 19–473 pg/mL) were significantly higher ($P = .0003$) than the preoperative BNP concentrations of those who survived (median 58 pg/mL, 10th–90th percentile 12–275 pg/mL). In a proportional hazards regression model with adjustment for sex, ethnicity, institution, and the covariates shown in Table 4, preoperative BNP concentration independently predicted postoperative mortality (hazard ratio 1.89, 95% CI 1.08–3.33, $P = .026$). Addition of preoperative BNP significantly improved the model's ability to predict postoperative mortality, as indicated by significant changes in the generalized r^2 ($P = .003$) and the likelihood ratio statistics ($P = .024$). On the basis of receiver operating characteristic analysis, the 75th and 90th percentiles of preoperative BNP concentrations had high specificity but lower sensitivity for predicting 5-year postoperative mortality. The receiver operating characteristic curve and related specificities, sensitivities, positive and negative predictive values, and accuracies for the 75th and 90th percentile BNP cutoffs are shown in Figure 4. Survival was significantly

TABLE 3. Multivariable analysis of ventricular dysfunction after primary coronary artery bypass grafting

Predictor	With preoperative BNP in model (n = 843*; AIC = 553.05)			Without preoperative BNP in model (n = 843*; AIC = 556.88)		
	Odds Ratio	95% Confidence Interval	P value	Odds Ratio	95% Confidence Interval	P value
Preoperative BNP (log ₁₀)	1.92	1.12–3.29	.018	—	—	—
Preoperative left ventricular ejection fraction (%)	0.97	0.95–0.99	.0006	0.96	0.94–0.98	<.0001
Cardiopulmonary bypass ≥120 min	2.28	1.40–3.72	.001	2.35	1.45–3.81	.0006
Preoperative cardiac troponin I >0.1 μg/L	1.83	1.13–2.96	.013	2.11	1.33–3.35	.002
Preoperative diuretic	1.7	1.02–2.85	.031	1.81	1.08–3.04	.025

BNP, B-type natriuretic peptide; AIC, Akaike information criterion. *One or more of the model's predictor variables were missing for 180 subjects who were therefore not included in this analysis.

predicted by both the 75th and 90th percentile preoperative BNP cutoffs ($P = .0003$ and 0.0016 , respectively; Figure 5).

Preoperative BNP and Established Risk Models for Mortality After Cardiac Surgery

We used three different statistical assessments of model performance to determine whether preoperative BNP data improved the ability of five established cardiac surgical risk models to predict 5-year postoperative mortality in our patients undergoing primary CABG (Table 5). Mortality predictions from all five risk models improved significantly

with the addition of preoperative BNP data, as determined by at least one statistical assessment of model performance. The improvement in the logistic EuroSCORE model, however, was seen only with marginal improvement in one assessment of model performance (generalized r^2).

Discussion

Significant morbidity is reported in 18% to 43% of patients undergoing CABG²⁹ and has important implications for health care costs, quality of life, and survival. Currently used cardiac surgical risk stratification models demonstrate only a modest ability to predict postoperative mortality.^{22–26,29} Consequently, there is a need for models that accurately predict specific major morbidity as well as mortality after cardiac surgery,^{22,25,29} because this may enable targeted implementation of therapeutic interventions. Although risk stratification models have traditionally incorporated clinical patient characteristics, there is increasing use of biomarkers in addition to clinical parameters, particularly for ambulatory populations.^{6–9} We investigated the benefit of adding preoperative BNP concentration to clinical patient characteristics to predict morbidity and mortality after primary CABG.

We found that preoperative BNP concentration independently predicted increased postoperative in-hospital ventricular dysfunction, hospital stay, and 5-year mortality after primary CABG, after adjustment for clinical predictors. This suggests that preoperative BNP is a useful addition to classically accepted clinical risk factors, such as preoperative myocardial infarction or low LVEF, for identifying patients at high risk for perioperative morbidity and mortality. Similar to findings in acute coronary syndrome populations,^{6–9} we found that preoperative BNP provided prognostic information for patients undergoing CABG that is additional to that provided by preoperative cTnI. Furthermore, to our knowledge, this study is the first to identify a predictive benefit of adding preoperative BNP data to multiple established cardiac surgical risk stratification models.

Most previous studies that have investigated preoperative BNP as a predictor of adverse events after cardiac surgery

BNP (pg/mL)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
141	50%	78%	23%	92%	75%
292	27%	92%	31%	91%	85%

Figure 3. Receiver operating characteristic curve describing preoperative plasma B-type natriuretic peptide (BNP) concentrations in relation to in-hospital ventricular dysfunction after primary coronary artery bypass grafting.

TABLE 4. Proportional hazards model of mortality during follow-up up to 5 years after primary coronary artery bypass grafting

Predictor	With preoperative BNP in model (n = 924*; AIC = 761.97)			Without preoperative BNP in model (n = 924*; AIC = 765.04)		
	Hazard Ratio	95% Confidence Interval	P value	Hazard Ratio	95% Confidence Interval	P value
Preoperative BNP (log ₁₀)	1.89	1.08–3.33	.026	—	—	—
Age (10-y increment)	1.71	1.30–2.26	.0001	1.84	1.40–2.42	<.0001
Smoking (>30 pack-y)	2.38	1.39–4.07	.002	2.50	1.46–4.27	.0008
Urgent procedure	1.85	1.05–3.25	.033	1.94	1.11–3.41	.021
Body mass index >30 kg/m ²	2.13	1.26–3.62	.005	1.93	1.15–3.25	.013
Preoperative angiotensin-converting enzyme inhibitor	0.58	0.34–0.99	.044	0.57	0.34–0.98	.042
Left ventricular ejection fraction (%)	0.98	0.96–1.00	.060	0.97	0.95–0.99	.005

BNP, B-type natriuretic peptide; AIC, Akaike information criterion. *One or more of the model's predictor variables were missing for 99 subjects who were therefore not included in this analysis.

have been underpowered. Univariate analyses have shown that preoperative BNP predicts such adverse outcomes as postoperative LVEF,^{11,12} inotrope requirements,¹¹ mechanical ventricular support,¹⁵ postoperative cTnI concentration,¹³ hospital stay,¹⁵ and mortality.^{13,15} A prospective study of patients undergoing CABG or valve surgery found that preoperative and POD 1 BNP concentrations predicted postoperative CHF and 1-year survival in univariate analysis; however, that study did not assess preoperative BNP in multivariable

analysis. After statistical adjustment for preoperative LVEF, POD 1 BNP concentration no longer predicted postoperative CHF or mortality.¹⁴ Another, smaller study reported that

BNP (pg/mL)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
141	43%	82%	24%	91%	74%
292	19%	92%	32%	90%	86%

Figure 4. Receiver operating characteristic curve describing preoperative plasma B-type natriuretic peptide (BNP) concentrations in relation to 5-year mortality after primary coronary artery bypass grafting.

Figure 5. Kaplan–Meier survival curves for all patients to 5 years after surgery, stratified by preoperative B-type natriuretic peptide (BNP) greater than 292 pg/mL versus less than or equal to 292 pg/mL (A) and by preoperative B-type natriuretic peptide greater than 141 pg/mL versus less than or equal to 141 pg/mL (B). Vertical bars indicate 95% confidence intervals for survival estimates for each year of postoperative follow-up.

TABLE 5. Effect of adding preoperative B-type natriuretic peptide level to known risk models for mortality after coronary artery bypass grafting

Risk score	AIC		−2 log Likelihood			r ² (%)		
	Without	With	Without	With	P value*	Without	With	P value†
Cleveland Clinic	662.556	661.683‡	660.556	657.683	.09	5.21	5.78‡	.016
EuroSCORE								
Additive	667.831	666.141‡	665.831	662.141	.055	3.95	4.69‡	.007
Logistic	659.744	659.805	657.744	655.805	.164	5.56	5.94‡	.048
New York State	679.132	671.661‡	677.132	667.661‡	.002	1.73	3.63‡	<.0001
Modified Parsonnet	591.846	587.316‡	589.846	583.316‡	.011	2.06	3.54‡	.0003

Assessed with proportional hazards models, with the outcome being all-cause mortality during up to 5-year postoperative follow-up. Lower values of Akaike information criterion and likelihood ratio statistic and higher values of r^2 indicate better fit. Because there are numerous methods for comparing global measures of fit for predictive models, we chose three well-established statistical methods that have penalties for adding variables and for overfitting models. AIC, Akaike information criterion. *Comparison of nested models under χ^2 statistic with 1 degree of freedom. †Comparison of F statistic of nested models computed with Nagelkerke r^2 (%). ‡Superior fit in comparison of models with or without inclusion of log₁₀ preoperative B-type natriuretic peptide concentration.

preoperative BNP predicted 2-year postoperative survival after adjustment for preoperative LVEF, Cleveland Clinic risk score, and postoperative cTnI concentration.¹³

We determined a preoperative BNP concentration cutoff of greater than 292 pg/mL to be highly specific for development of postoperative ventricular dysfunction and longer-term (up to 5-year) mortality. The utility of a BNP cutoff of 292 pg/mL for patients undergoing primary CABG is further supported by significantly decreased survival demonstrated in Kaplan–Meier survival curves stratified by the preoperative BNP 292 pg/mL cutoff. The BNP concentration cutoff in the literature for diagnosing ambulatory CHF is approximately 100 to 200 pg/mL,^{3,4} with a 35% increase in relative risk of death for each 100-pg/mL increment in BNP concentration.⁵ The higher preoperative BNP cutoff of 292 pg/mL, relative to the cutoff for diagnosing CHF in ambulatory patients, is likely related to greater incidences of both preoperative myocardial ischemia and heart failure in patients undergoing CABG. The 292 pg/mL preoperative BNP cutoff is similar to but somewhat lower than the preoperative BNP cutoff of greater than 385 pg/mL found by Hutfless and associates¹⁵ to predict 1-year mortality in 98 male patients undergoing CABG, some of whom underwent concurrent valve surgery.

We used five risk scoring systems initially developed to predict in-hospital or 30-day postoperative cardiac surgical mortality. These five risk models have also been shown to best predict 1-year mortality in CABG surgical populations.²⁶ Because our study was underpowered to examine 1-year mortality, we assessed these models' abilities to predict up to 5-year all-cause mortality with the addition of preoperative BNP concentration. Four of these five mortality risk stratification models showed significant improvements in at least two of three mortality risk prediction measures when preoperative BNP concentration was added. The improvement in the logistic EuroSCORE model,²⁴ however, was seen with only one assessment of model performance. Overall, these findings support our observation from Cox

proportional hazard modeling that preoperative BNP concentration is an important predictor of postoperative mortality. One reason that mortality prediction did not improve substantially with the addition of preoperative BNP concentration to the EuroSCORE logistic regression model²⁴ may be that this model was better than the other four models at predicting 5-year postoperative mortality in our primary CABG population. Alternatively, the EuroSCORE logistic regression model may include or more heavily weight covariates that have some collinearity with preoperative BNP concentration, thus reducing the value of adding preoperative BNP concentration to this model. The EuroSCORE logistic model's inclusion of such covariates as reoperative CABG or other previous or concurrent cardiac or thoracic aortic surgeries, emergency surgery, endocarditis, and critical preoperative state suggests that further investigation may be warranted to assess the value of preoperative BNP for predicting mortality in cardiac surgical populations that are at higher risk than our primary CABG population.

We also observed that plasma BNP concentration declined after POD 3 in patients who did not have postoperative ventricular dysfunction but remained elevated at least through POD 5 in patients who did have ventricular dysfunction. Postoperative BNP concentrations have been shown to predict long-term morbidity and mortality in cardiac¹⁴ and vascular³⁰ surgical populations. In ambulatory patients with CHF, aggressive administration of β -blockers and angiotensin-converting enzyme inhibitors to reduce plasma BNP concentrations below 100 pg/mL has been shown to decrease CHF-related hospitalizations and mortality.³¹ Thus there may be a role for peak postoperative BNP in discriminating surgical patients who might benefit from aggressive postoperative therapeutic interventions. Further research is warranted to determine whether BNP concentrations after cardiac surgery are useful for assessing cardiac function, targeting postoperative medical therapies, and predicting long-term morbidity and mortality.

Limitations

Several potential limitations of our study deserve consideration. First, this study included only patients undergoing non-emergency primary CABG alone with CPB. Consequently, caution should be exercised in extrapolating these findings to other cardiac surgical populations, including patients with cardiac valve disease. Second, although we adjusted for institution in our multivariable analyses, we cannot entirely rule out nonspecific biases introduced by institutional variations in intraoperative and postoperative management. Furthermore, we cannot rule out potential bias from individual practice variations introduced by including multiple surgeons in this study. Third, there is no standardized outcome definition for ventricular dysfunction after cardiac surgery to guide our study's ventricular dysfunction outcome definition. Many patients undergoing primary CABG at both study institutions do not have perioperative monitoring with transthoracic echocardiography or pulmonary arterial catheterization. We therefore elected to define ventricular dysfunction after CABG as either a need for two or more inotropes or new IABP or VAD support to ensure that we were not including patients with normal ventricular function. It is not standard organizational or surgeon-based practice at either institution to separate the patient from CPB with prophylactic inotropic support. Furthermore, we believe that the significant associations we observed between our ventricular dysfunction outcome and both extended postoperative hospital stay and 5-year mortality reinforce the importance of our in-hospital postoperative ventricular dysfunction outcome. Fourth, there are multiple available plasma BNP assays, and the numeric cut points we found should be considered specific to the analysis platform used in this study.

In light of the high specificity but lower sensitivity of preoperative BNP concentration cutoffs both in our study and in that of Hutfless and associates,¹⁵ we believe that preoperative BNP should be used in conjunction with other clinical predictors delineated in the multivariable models that we established for postoperative ventricular dysfunction, hospital stay, and mortality. Importantly, our results should not be interpreted as meaning that elevated BNP is predictive of poorer perioperative outcome in the absence of preoperative cardiovascular compromise. Rather, preoperative BNP may help discriminate patients who have marginal cardiovascular reserve despite ambiguous clinical symptoms. Although our results suggest that patients undergoing primary CABG who have elevated preoperative BNP concentrations might benefit from a delay in surgery to allow better preoperative medical optimization and perioperative planning, this topic needs to be investigated in future studies.

Conclusions

Our findings support the use of preoperative BNP concentrations along with other clinical predictors to identify patients

at risk for in-hospital ventricular dysfunction, longer hospital stay, and longer-term (up to 5-year) all-cause mortality after primary CABG with CPB. Additional studies are needed to assess assay-specific perioperative BNP cutoffs for risk prediction in both patients undergoing primary CABG and other cardiac surgical groups and to evaluate the efficacy of interventions such as delaying surgery for medical optimization on the basis of elevated preoperative BNP concentrations.

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