Increased Peak Postoperative B-type Natriuretic Peptide Predicts Decreased Longer-term Physical Function after Primary Coronary Artery Bypass Graft Surgery

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ABSTRACT

Background: Increased peak postoperative B-type natriuretic peptide (BNP) is associated with increased major adverse cardiovascular events and all-cause mortality after coronary artery bypass graft (CABG) surgery. Whether increased postoperative BNP predicts worse postdischarge physical function (PF) is unknown. We hypothesized that peak postoperative BNP associates with PF assessed up to 2 yr after CABG surgery, even after adjusting for clinical risk factors. including preoperative PF.

Methods: This two-institution prospective cohort study included patients undergoing primary CABG surgery with cardiopulmonary bypass. Short Form-36 questionnaires were administered to subjects preoperatively and 6 months, 1 yr, and 2 yr postoperatively. Short Form-36 PF domain scores were calculated using the Short Form-36 norm–based scoring algorithm. Plasma BNP concentrations measured preoperatively and on postoperative days 1–5 were $\log_{10}$ transformed before analysis. To determine whether peak postoperative BNP independently predicts PF scores 6 months through 2 yr after CABG surgery, multivariable longitudinal regression analysis of the postoperative PF scores was performed, adjusting for important clinical risk factors.

Results: A total of 845 subjects (mean ± SD age, 65 ± 10 yr) were analyzed. Peak postoperative BNP was significantly associated with postoperative PF (effect estimate for $\log_{10}$ peak BNP, −7.66 PF score points [95% CI, −9.68 to −5.64]; $P = <0.0001$). After multivariable adjustments, peak postoperative BNP remained independently associated with postoperative PF (effect estimate for $\log_{10}$ peak BNP, −3.06 PF score points [95% CI, −5.15 to −0.97]; $P = 0.004$).

Conclusions: Increased peak postoperative BNP independently associates with worse longer-term PF after primary CABG surgery. Future studies are needed to determine whether medical management targeted toward reducing increased postoperative BNP can improve PF after CABG surgery.

What We Already Know about This Topic

- Increased B-type natriuretic peptide concentration after cardiac surgery predicts major adverse cardiovascular outcomes, but its correlation with long-term functional status is unknown.

What This Article Tells Us That Is New

- In greater than 800 patients undergoing coronary artery bypass grafting, an increased peak postoperative B-type natriuretic peptide concentration was associated with worse long-term function 6 months to 2 yr after surgery.

IN the United States alone, almost 250,000 patients undergo coronary artery bypass graft (CABG) surgery annually, with a primary goal to prevent major adverse cardiovascular events, including death.[1] With percutaneous

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coronary interventions and advances in medical management shifting primary CABG surgery to progressively older ages, health-related quality of life (HRQL) after CABG surgery is increasingly relevant.[2,3] For most patients undergoing CABG surgery, postoperative HRQL improves or at least remains the same as before surgery; however, 7–24% of patients who undergo CABG surgery report significant deterioration in HRQL during the years after surgery.[4–8] Identifying modifiable perioperative risk factors for declines in HRQL after CABG surgery could facilitate treatments and interventions targeted toward improving postoperative functional status and associated morbidity and mortality.

Plasma B-type natriuretic peptide (BNP) is secreted primarily by cardiac ventricular myocytes in response to increased ventricular wall stress generated by volume or pressure overload or ischemia.[9,10] BNP is an established prognostic biomarker in both patients who experience ambulatory heart failure and those who have acute coronary syndrome.[10–18] Several studies[19–22] of BNP-guided (or N-terminal pro-BNP–guided) chronic heart failure treatment interventions suggest corresponding reductions in adverse cardiac events. In the setting of CABG surgery, increased BNP measures during the early days after surgery are significantly associated with more frequent in-hospital adverse cardiovascular events, longer hospital stays, and increased incidence of major adverse cardiovascular events and all-cause mortality after discharge.[23–28] However, whether increased postoperative BNP predicts significant declines in physical function (PF) during the first several years after CABG surgery is unknown.

By using a prospectively enrolled cohort of patients undergoing isolated primary CABG with cardiopulmonary bypass (CPB), we sought to determine whether increased peak postoperative plasma BNP is associated with significantly lower Short Form-36 (SF-36) Health Survey PF domain scores, assessed 6 months to 2 yr after surgery. We hypothesized that this association would remain significant even after adjusting for the preoperative PF domain score and other clinical risk factors.

Materials and Methods

Study Population

Between August 27, 2001, and September 20, 2006, 1,519 men and women (aged 20–89 yr) scheduled for isolated primary CABG surgery with CPB at Brigham and Women's Hospital, Boston, Massachusetts, and the Texas Heart Institute, St Luke's Episcopal Hospital, Houston, Texas, were enrolled prospectively into an ongoing study known as the CABG Genomics Program (information available at: http://clinicaltrials.gov/show/NCT00281164; last updated July 10, 2009). Institutional Review Board approvals (Partners Institutional Review Board, Boston; and St Luke's Episcopal Hospital Institutional Review Board) and subject written informed consent were obtained. CABG Genomics Program exclusion criteria include a preoperative hematocrit lower than 25% or transfusion of leukocyte-rich blood products within 30 days before surgery. Enrolled subjects were prospectively excluded from analysis for this study if they had undergone previous cardiac surgery; if they underwent emergency surgery or concurrent valve surgery; if they received a preoperative inotrope, intraaortic balloon pump, or ventricular assist device support; if they underwent CABG surgery without CPB or an aortic cross clamp; or if they were missing preoperative or peak postoperative plasma BNP measurements. Patients with severe renal dysfunction (requiring preoperative hemodialysis or having a preoperative serum creatinine concentration greater than 3 mg/dl) were excluded from analysis because severe renal dysfunction and perioperative dialysis can variably affect perioperative plasma BNP concentrations.[29,30] In addition, subjects were excluded if they were missing either preoperative or all three postoperative SF-36 PF domain scores.

Data and Blood Collection

Data regarding preoperative demographic characteristics, comorbidities and medications, surgical characteristics, and postoperative in-hospital events were collected for each enrolled subject during his or her primary hospitalization using a detailed case report form. Postoperative patient survival was assessed by mail, telephone interviews, and examinations of the Social Security Death Index through May 2009. Plasma samples were obtained preoperatively and on postoperative days (PODs) 1–5 and were stored in vapor phase liquid nitrogen until analysis. BNP and cardiac troponin I concentrations were measured for all samples as a single batched analysis at a single core laboratory using sandwich immunoassay (Triage® platform; Biosite, San Diego, CA). These biomarker assays were conducted after subjects were discharged from primary surgical hospitalization and were not available during patient care.

The HRQL assessments were conducted preoperatively and 6 months, 1 yr, and 2 yr after surgery using the SF-36 Health Survey questionnaire (SF-36v2®), version 2 (short-term 1-week recall was measured).[31] To avoid confounding the assessment of perioperative predictors of longer-term postoperative PF by other significant postoperative life factors that could influence PF (*e.g.*, advancing age), we limited our analysis to 2 yr of follow-up. Postoperative questionnaires were distributed by mail. If a questionnaire was not returned, a second questionnaire was mailed to the subject or the questionnaire was administered to the subject over the telephone. Raw SF-36 questionnaire response data were scored using the SF-36 maximal data estimation computerized scoring algorithm.[31] Per standard practice, we analyzed the normative-based scores produced by SF-36 scoring (1998 US population-adjusted normative scores: population mean score, 50; 10-point score change representing an SD of 1).[31]

The SF-36 questionnaire is a validated HRQL assessment instrument that evaluates eight health domains: PF (10 questions), role physical (RP; 4 questions), bodily pain, general health, vitality, social functioning, role emotional, and mental health. The PF domain questions assess limitations in physical functioning across a range of activities, including bathing, walking, climbing stairs, carrying groceries, and participating in strenuous sports. The RP domain questions assess how physical health limits ability to accomplish work-related or other usual activities. The physical component summary (PCS) and mental component summary scores aggregate information from all eight health domains using principal component analysis, with the PF, RP, and bodily pain domains contributing the most to the PCS score.[31] We prospectively identified the postoperative PF domain score as the primary study outcome because of our belief that the biologic features underlying increased BNP (*i.e.*, distressed myocardium) are likely to associate most with decreased PF. The RP domain and PCS scores were also identified prospectively as secondary outcomes because these assessments should reflect aspects of postoperative PF. We chose the period from 6 months to 2 yr after surgery to represent PF after recovery from CABG surgery and used methods for analysis of repeated measurements to estimate a constant association between peak postoperative BNP and PF during this period.

Definitions

Peak postoperative BNP (the primary study predictor) and other predictor covariates were defined prospectively. Peak postoperative plasma BNP was assessed if a subject had at least three of the daily POD 1–5 measures and was defined as the highest POD 1–5 BNP value. We selected this definition of peak postoperative BNP because plasma BNP concentrations tend to increase significantly during PODs 1–3 and then plateau during PODs 3–5.[32] Therefore, even for subjects discharged on POD 4, the highest of three postoperative measures is likely to closely approximate the peak concentration of BNP during the first 5 PODs.

Postoperative creatinine clearance was estimated using the highest of the routine postoperative creatinine measures obtained during primary hospitalization. Postoperative ventricular dysfunction was defined as a new requirement for two or more inotropes or new placement of an intraaortic balloon pump or ventricular assist device either during the intraoperative period after the patient separated from CPB or postoperatively in the intensive care unit. Inotrope support was defined as continuous infusion of amrinone, milrinone, dobutamine, dopamine (more than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), epinephrine, isoproterenol, norepinephrine, or vasopressin.

Statistical Analyses

Statistical analyses were performed using computer software (R, version 2.11.1; R Foundation for Statistical Computing, Vienna, Austria). Mean baseline, 6-month, 1-yr, and 2-yr PF domain scores were compared between pairs of points using the paired *t* test. Stepwise selection from table 1 variables (*P* value thresholds for model entry and exit were 0.15 and 0.05, respectively) was used to identify variables in multivariable logistic regression that strongly predicted subjects who were excluded from analysis secondary to missing preoperative or postoperative PF scores (n = 338) *versus* included subjects (n = 845). Univariate comparisons of table 1 characteristics for these excluded and included subjects were performed using a χ^2, Fisher exact, or Wilcoxon rank sum test, as appropriate. *P* value assessments for all study analyses were two tailed.

The SF-36 domain and component summary scores assessed 6 months, 1 yr, and 2 yr after CABG surgery were analyzed using linear models for repeated measurements, assuming a between-subjects variance, a within-subjects (error) variance, and three unrestricted correlation parameters for the within-subjects errors.[33] We used this longitudinal regression analysis approach because SF-36 assessments of each subject at three postoperative points are not statistically independent. Model parameters were estimated by restricted maximum likelihood estimation. We assumed that the association between peak postoperative BNP and PF remained constant during the 6-month to 2-yr postoperative period; the coefficient of $\log_{10}$ peak postoperative BNP in our models estimates this constant association. Because continuous plasma BNP and cardiac troponin I values were right skewed, these variables were $\log_{10}$ transformed before regression analyses. Univariate analyses were performed to assess associations between demographic and clinical characteristics (table 1) and postoperative PF domain scores.

To develop a multivariable model for postoperative PF, age (dichotomized at 65 yr), sex, institution, and ethnicity were forced into the multivariable model before performing forward-and-backward stepwise selection of the remaining covariates from the variables shown in table 1. Variable selection for the multivariable model was based on best stepwise reduction in Bayes Information Criterion (BIC). Peak postoperative BNP was then added to the final BIC-derived multivariable model to assess its additional value for predicting postoperative PF. The Wald test and its associated CI were used to assess the statistical significance of peak postoperative BNP in the multivariable model. BIC is a statistical criterion used to assess how well multivariable regression models containing data from the same patients predict an outcome. A multivariable model is considered better for predicting an outcome if it has a lower BIC. The BIC is more conservative than the other commonly used criterion, the Akaike Information Criterion, for adding variables to a multivariable model. Therefore, to avoid model overfitting, we used the BIC instead of the Akaike Information Criterion to select variables for inclusion in the final multivariable prediction model.

Although they dropped out of the multivariable model during stepwise selection, preoperative left ventricular ejection fraction, peak postoperative cardiac troponin I, and postoperative creatinine clearance covariates were individu-

Table 1. Univariate Associations between Perioperative Clinical Risk Factors and Postoperative SF-36 Questionnaire Physical Function Domain Scores Assessed 6 Months through 2 yr after Primary CABG Surgery

Predictor Variables (n = 845)	Value	Effect Estimate (95% CI)	*P* Value
Demographics and Preoperative Risk Factors			
Age ≥65 yr	420 (49.7)*	−4.07 (−5.31 to −2.82)	<0.0001
Female Sex	163 (19.3)*	−5.26 (−6.84 to −3.68)	<0.0001
Institution			
Brigham and Women's Hospital	694 (82.1)*	Reference Group	Reference Group
Texas Heart Institute	151 (17.9)*	0.37 (−1.30 to 2.05)	0.66
Ethnicity (Minority)	94 (11.1)*	−1.42 (−3.47 to 0.62)	0.17
Preoperative SF-36 Physical Function Domain Score*	42.1 ± 11.5†	0.36 (0.31 to 0.41)	<0.0001
Diabetes Mellitus (n = 844)	238 (28.2)*	−3.51 (−4.91 to −2.11)	<0.0001
Hypertension (n = 843)	628 (74.3)*	−1.89 (−3.36 to −0.43)	0.01
Hypercholesterolemia (n = 841)	642 (76.0)*	1.02 (−0.49 to 2.53)	0.19
Obesity (BMI >30 kg/m^2)	320 (37.9)*	−3.43 (−4.73 to −2.13)	<0.0001
Smoking (>30–Pack Year History) (n = 816)	224 (26.5)*	−3.37 (−4.81 to −1.93)	<0.0001
Preoperative Creatinine Clearance, ml · min^{-1} · 1.73 m^{-2}	74 ± 19†	0.06 (0.02 to 0.09)	0.0008
Myocardial Infarction ≤2 wk Preoperatively (n = 844)	149 (17.6)*	−2.00 (−3.69 to −0.32)	0.02
Left Ventricular Ejection Fraction, % (n = 816)	53 ± 12†	0.10 (0.05 to 0.15)	0.0001
No. of Coronary Artery Regions with >50% Stenosis			
0–1	53 (6.3)*	Reference Group	Reference Group
2	281 (33.3)*	0.53 (−2.26 to 3.32)	0.71
3	511 (60.5)*	1.19 (−1.50 to 3.88)	0.39
Moderate or Severe Mitral Insufficiency (n = 819)	16 (1.9)*	−5.78 (−10.49 to −1.06)	0.02
Past Arrhythmia	83 (9.8)*	−1.92 (−4.06 to 0.23)	0.08
Anemia	288 (34.1)*	−3.59 (−4.92 to −2.27)	<0.0001
Preoperative BNP, pg/ml	17.6 (4.9–50.4)‡	−1.89 (−2.51 to −1.26), for $\log_{10}$ increase	<0.0001
Preoperative cTnI >0.1 μg/l	127 (15.0)*	−1.78 (−3.57 to 0.004)	0.05
Preoperative Medications			
ACE inhibitor (n = 844)	388 (45.9)*	−0.03 (−1.31 to 1.26)	0.97
Diuretic	178 (21.1)*	−3.73 (−5.28 to −2.18)	<0.0001
Statin	659 (78.0)*	0.75 (−0.78 to 2.29)	0.34
Digoxin	24 (2.8)*	−5.08 (−8.93 to −1.22)	0.01
β-Blocker	670 (79.3)*	0.78 (−0.80 to 2.36)	0.33
Calcium Channel Blocker	114 (13.5)*	−3.14 (−4.99 to −1.29)	0.0009
Aspirin	651 (77.0)*	0.61 (−0.91 to 2.13)	0.43
Nonaspirin Platelet Inhibitor	164 (19.4)*	−2.09 (−3.71 to −0.48)	0.01
Intravenous Nitroglycerin (n = 842)	89 (10.5)*	−0.46 (−2.55 to 1.63)	0.67
Intravenous Heparin	199 (23.6)*	−0.59 (−2.09 to 0.92)	0.44
Surgical Risk Factors			
Urgent Surgery	466 (55.1)*	−1.56 (−2.84 to −0.28)	0.02
Cardiopulmonary Bypass Time >120 min	200 (23.7)*	1.05 (−0.46 to 2.55)	0.17
No. of Coronary Grafts (n = 844)			
<3	122 (14.4)*	Reference Group	Reference Group
3	390 (46.2)*	−0.03 (−1.95 to 1.89)	0.97
>3	332 (39.3)*	1.73 (−0.23 to 3.69)	0.08
In-Hospital Postoperative Outcomes			
Ventricular Dysfunction	94 (11.1)*	−5.48 (−7.49 to −3.47)	<0.0001
New-Onset Atrial Fibrillation	260 (30.8)*	−1.35 (−2.74 to 0.03)	0.05
Postoperative Creatinine Clearance, ml · min^{-1} · 1.73 m^{-2} (n = 844)	68 ± 21†	0.09 (0.06 to 0.12)	<0.0001
Peak Postoperative cTnI, μg/l	1.34 (0.66–2.84)‡	−1.91 (−3.09 to −0.73), for $\log_{10}$ increase	0.002

The SF-36 questionnaire physical function domain score is a normative based score derived by SF-36 version 2 acute 1-wk recall scoring algorithm based on 1998 US population-adjusted normative scores (population mean score, 50; a 10-point change in score represents an SD of 1). Postoperative SF-36 physical function domain scores were assessed at 6 months, 1 yr, and 2 yr after CABG surgery.

* Data are given as number (percentage) (dichotomous variables). † Data are given as mean ± SD (continuous variables). ‡ Data are given as median (25th-75th percentile) (continuous variables).

ACE = angiotensin-converting enzyme; BMI = body mass index; BNP = B-type natriuretic peptide; CABG = coronary artery bypass graft; cTnI = cardiac troponin I; SF = Short Form.

Table 2. Multivariable Longitudinal Regression Model for Predicting SF-36 Physical Function Domain Scores Assessed 6 Months through 2 yr after Primary Coronary Artery Bypass Graft Surgery

	Model			
	With Log_{10} Peak Postoperative BNP (BIC = 12661.90)		Without Log_{10} Peak Postoperative BNP (BIC = 12664.58)	
Predictors	Effect Estimate (95% CI)	*P* Value	Effect Estimate (95% CI)	*P* Value
Log_{10} Peak Postoperative BNP	−3.06 (−5.15 to −0.97)	0.004	NA	NA
Preoperative SF-36 Physical Function Domain Score	0.26 (0.21 to 0.31)	<0.0001	0.27 (0.22 to 0.32)	<0.0001
Aged ≥65 yr	−3.21 (−4.39 to −2.03)	<0.0001	−3.62 (−4.77 to −2.47)	<0.0001
Female Sex	−2.17 (−3.63 to −0.70)	0.004	−2.55 (−4.00 to −1.11)	0.0006
Institution	−1.05 (−2.62 to 0.51)	0.19	−0.64 (−2.19 to 0.91)	0.42
Minority	−1.78 (−3.58 to 0.03)	0.05	−1.73 (−3.54 to 0.09)	0.06
Obesity (BMI >30 kg/m^2)	−2.60 (−3.79 to −1.41)	<0.0001	−2.36 (−3.55 to −1.18)	0.0001
Diabetes Mellitus	−1.78 (−3.03 to −0.53)	0.005	−1.92 (−3.17 to −0.67)	0.003
Smoking (>30–Pack Year History)	−2.21 (−3.48 to −0.93)	0.0007	−2.41 (−3.68 to −1.14)	0.0002
Preoperative Diuretic	−1.60 (−2.99 to −0.21)	0.02	−1.81 (−3.20 to −0.42)	0.01
Postoperative Ventricular Dysfunction	−2.79 (−4.65 to −0.94)	0.003	−3.43 (−5.24 to −1.62)	0.0002

Data are for 815 subjects (30 subjects were missing one or more of the model's predictor variables and were not included in the analysis).

BIC = Bayesian Information Criteria; BMI = body mass index; BNP = B-type natriuretic peptide; NA = not applicable; SF = Short Form.

ally forced back into the final BIC-derived multivariable prediction model because of perceived potential for these covariates to confound associations between peak postoperative BNP and postoperative PF. However, this resulted in no meaningful change in the effect estimate or *P* value for this association; therefore, these variables were not included in the final multivariable prediction model. We did not adjust for point of follow-up questionnaire assessment within our repeated-measures regression model because this did not significantly improve model fit compared with the simpler regression model that assumed a constant association between peak postoperative BNP and PF scores during the 6-month to 2-yr postoperative period.

We repeated the multivariable modeling approaches described for the postoperative PF outcome to assess whether peak postoperative BNP independently predicts the secondary RP domain and PCS score outcomes. To assess potential effect modification of the association between peak postoperative BNP and longitudinal SF-36 outcomes by age, we added an age of 65 yr or older by peak postoperative BNP interaction term into the final multivariable PF, RP, and PCS prediction models, along with peak postoperative BNP.

A sensitivity analysis based on multiple imputation was performed to assess the potential for bias arising from exclusion of subjects who were missing all three postoperative PF scores. For the 221 subjects surviving 6 months after surgery who had preoperative PF scores but no postoperative PF scores, simulated 6-month, 1-yr, and 2-yr follow-up PF scores were generated for each subject using the regression model shown in table 2 and assuming hypothetical values of the regression coefficient for log_{10} peak postoperative BNP for these subjects equaling 0%, 20%, 40%, 60%, 80%, and 100% of the regression coefficient (−3.06) estimated from the available data. A total of 100 postoperative PF score data sets were created for each of the six hypothetical regression coefficient values, and regression coefficients and corresponding SEs for log_{10} peak postoperative BNP were then estimated for each of the six scenarios by multiple imputation.[34] This analysis provided information about the sensitivity of our findings to different potential relationships between log_{10} peak postoperative BNP and postoperative PF scores in subjects who were excluded from analysis for lack of follow-up.

Results

Subject Exclusions and Postoperative Follow-up

Figure 1 outlines subject exclusions and availability of PF domain scores. As previously reported, of the 1,519 subjects enrolled into the CABG Genomics Program during the study period, 336 were excluded from analysis according to prospectively defined clinical and biomarker–related criteria.[32] An additional 103 subjects were excluded because of missing preoperative SF-36 PF domain scores. Of the remaining 1,080 subjects who were eligible for analysis, 845 (78.2%) provided PF domain scores for 6-month, 1-yr, or 2-yr follow-up and, thus, were included in this analysis. Seventeen of the subjects who were not analyzed secondary to missing postoperative PF score data had died before the 6-month follow-up.

Compared with the analyzed subjects, patients excluded for missing PF score data were significantly ($P < 0.05$) younger (mean ± SD, 61 ± 10 yr); had higher preoperative creatinine clearance (mean ± SD, 77 ± 24 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$); and were more likely to be minorities (28.4%), to have a body mass index greater than 30 kg/m^2 (44.7%), to undergo longer than 120 min of CPB (16.9%), to have received a preoperative non-

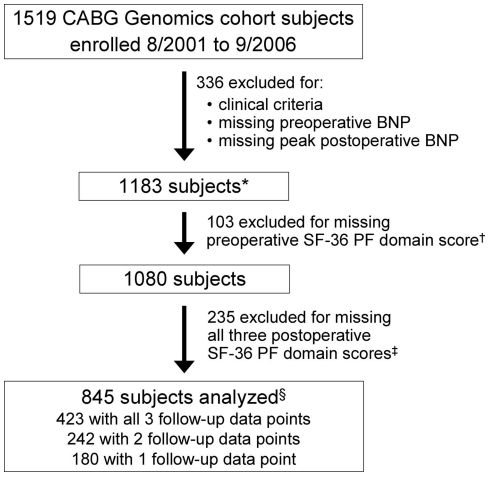

Fig. 1. This diagram outlines subject exclusions from the CABG Genomics Program cohort for this study. *A total of 47 (4.0%) of the 1,183 subjects eligible for analysis died during the 2-yr study follow-up; 17 of these subjects died before the 6-month follow-up. †Of the 103 subjects excluded for missing preoperative physical function (PF) score data, three died before the 6-month follow-up and two died between the 1- and 2-yr follow-up. ‡Of the 235 subjects excluded for having no follow-up postoperative PF score, 14 died before the 6-month follow-up, 9 died between the 6-month and 1-yr follow-up, and 5 died between the 1- and 2-yr follow-up. §Of the 845 analyzed subjects, 2 died between the 6-month and 1-yr follow-up and 12 died between the 1- and 2-yr follow-up. BNP = B-type natriuretic peptide; CABG = coronary artery bypass graft; SF = Short Form.

aspirin platelet inhibitor (27.5%), or to have not received a preoperative β-blocker (28.1%). The group missing PF scores also developed significantly less postoperative atrial fibrillation (23.7%), was more frequently enrolled at one of the study institutions (45.3%), and had lower preoperative (mean ± SD, 41.9 ± 86.0 pg/ml) and peak postoperative (mean ± SD, 211.9 ± 192.3 pg/ml) BNP measures. Multivariable logistic regression conducted using stepwise selection from table 1 variables indicated that the independent predictors of subjects without analyzable PF score data were institution of enrollment ($P < 0.0001$), minority ethnicity ($P < 0.0001$), need for urgent surgery ($P = 0.01$), and not developing postoperative atrial fibrillation ($P = 0.02$).

Preoperative and Postoperative Follow-up PF Domain Scores

As shown in figure 2, postoperative 6-month, 1-yr, and 2-yr PF domain scores were significantly improved compared with preoperative PF domain scores ($P < 0.0001$). The PF domain scores did not differ significantly between 6 months and 1 yr after surgery ($P > 0.05$), but the scores did decline significantly between postoperative years 1 and 2 ($P = 0.0001$).

Univariate Associations between Patient Characteristics and Postoperative PF

Demographic, medical, and surgical characteristics of the analyzed study subjects are shown in table 1, along with each

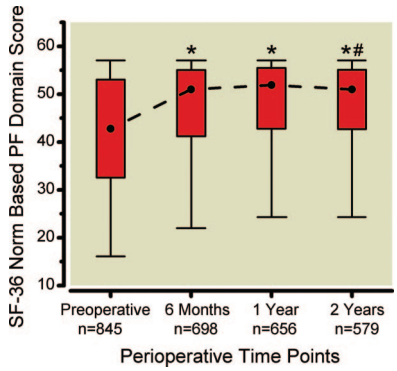

Fig. 2. Preoperative and 6-month, 1-yr, and 2-yr postoperative Short Form-36 norm-based physical function domain scores for 845 subjects undergoing primary coronary artery bypass graft surgery. The lower and upper borders of the box plots represent the 25th and 75th percentile values, and the ends of the upper and lower whiskers represent the 10th and 90th percentile values. The dashed line connects the median values for preoperative and follow-up points. * Significantly higher than preoperative baseline ($P < 0.0001$). # Significantly lower than previous postoperative point ($P = 0.0001$). PF = physical function; SF = Short Form.

characteristic's univariate association with postoperative PF domain scores. The mean ± SD of the age of this subject group was 65 ± 10 yr. Subject characteristics with the strongest univariate associations with postoperative PF domain scores were preoperative PF domain score, postoperative ventricular dysfunction, female sex, and preoperative age 65 yr or older.

Univariate Associations between Peak Postoperative BNP and Postoperative SF-36 Scores

The median peak postoperative BNP concentration was 191.3 pg/ml (interquartile range, 120.1–319.2 pg/ml). The mean ± SD peak postoperative BNP was 260.3 ± 241.5 pg/ml. A univariate assessment of associations between peak postoperative BNP and the 10 SF-36 postoperative outcome scores are shown in table 3. As hypothesized, increased peak postoperative BNP was strongly associated with postoperative PF domain score (effect estimate, −7.66; 95% CI, −9.68 to −5.64; $P < 0.0001$) and was strongly associated with postoperative RP domain (effect estimate, −5.38; 95% CI, −7.34 to −3.42; $P < 0.0001$) and PCS (effect estimate, −6.19; 95% CI, −8.17 to −4.22) scores. Peak postoperative BNP was not associated with the postoperative mental health domain or the mental health summary score ($P > 0.05$).

Multivariable-adjusted Association between Peak Postoperative BNP and Postoperative PF Domain Scores

We further assessed the value of peak postoperative BNP concentration for predicting postoperative PF scores after adjusting for demographic characteristics (*i.e.*, aged 65 yr or older, sex, institution, and minority status) and other clinical predictors, including preoperative PF score, obe-

Table 3. Univariate Associations between Log_{10} Peak Postoperative BNP and SF-36 Domain and Component Summary Scores Assessed 6 Months through 2 yr after Primary Coronary Artery Bypass Graft Surgery*

SF-36 Variables	Score, Mean ± SD†	Effect Estimate (95% CI)‡	*P* Value‡
Domain Scores			
Physical Function (n = 845)	47.5 ± 9.6	−7.66 (−9.68 to −5.64)	<0.0001
Role Physical (n = 837)	48.6 ± 9.2	−5.38 (−7.34 to −3.42)	<0.0001
Bodily Pain (n = 842)	52.8 ± 8.9	−2.72 (−4.63 to −0.81)	0.005
General Health (n = 844)	49.7 ± 9.1	−2.86 (−4.84 to −0.88)	0.005
Vitality (n = 842)	53.1 ± 9.0	−3.73 (−5.70 to −1.77)	0.0002
Social Functioning (n = 843)	51.5 ± 7.4	−1.66 (−3.23 to −0.09)	0.04
Role Emotional (n = 836)	49.4 ± 8.5	−3.36 (−5.17 to −1.55)	0.0003
Mental Health (n = 842)	52.2 ± 8.5	−0.76 (−2.63 to 1.10)	0.42
Summary Scores			
Physical Component (n = 837)	49.0 ± 9.2	−6.19 (−8.17 to −4.22)	<0.0001
Mental Component (n = 837)	52.5 ± 8.3	−0.08 (−1.90 to 1.73)	0.93

The eight SF-36 domain scores are normative-based scores derived using the SF-36 (version 2) short-term 1-wk recall scoring algorithm based on 1998 US population-adjusted normative scores (population mean score, 50; a 10-point change in score represents an SD of 1). Component summary scores are derived for subjects with at least seven of the eight domain scores using principal component analyses implemented by the SF-36 (version 2) short-term 1-wk recall scoring algorithm.

* Scores and associations were assessed using data from the 845 subjects who had 6-month, 1-yr, or 2-yr physical function domain scores. † Values available for 6-month, 1-yr, and 2-yr scores. ‡ Data were derived from longitudinal regression analysis of postoperative 6-month, 1-yr, and 2-yr data.

BNP = B-type natriuretic peptide; SF = Short Form.

sity (body mass index greater than 30 kg/m^2), longer than 30–pack year history of smoking, occurrence of postoperative ventricular dysfunction, diabetes mellitus, and preoperative diuretic use (table 2). Even after multivariable adjustments, increased peak postoperative BNP predicts lower postoperative PF scores (effect estimate, −3.06; 95% CI, −5.15 to −0.97; $P = 0.004$). When we added aged 65 yr or older by peak postoperative BNP interaction term to the multivariable model, the interaction term was not statistically significant ($P = 0.49$), suggesting no significant effect modification by age for the association between increased peak postoperative BNP and lower postoperative PF. The results of the sensitivity analysis indicated that, even assuming no association in the excluded subjects between log_{10} peak postoperative BNP and 6-month through 2-yr postoperative PF scores (regression coefficient, 0.00), the overall association between increased peak postoperative BNP and lower postoperative PF scores remained significant ($P < 0.05$) when the data from the excluded subjects were pooled with the data from the 845 analyzed subjects.

Multivariable-adjusted Association between Peak Postoperative BNP and Postoperative Role Physical Domain and PCS Scores

Increased peak postoperative BNP remained a significant predictor of lower postoperative RP domain scores after adjusting for demographic characteristics (aged 65 yr or older, sex, institution, and minority status) and other clinical predictors, including preoperative RP domain score, obesity (body mass index greater than 30 kg/m^2), myocardial infarction within 2 wk of surgery, greater than 30–pack year history of smoking, and preoperative diuretic use (effect estimate, −2.72; 95% CI, −4.93 to −0.52; $P = 0.02$). After adjusting for demographic characteristics and other clinical predictors, including preoperative PCS domain score, obesity (body mass index greater than 30 kg/m^2), diabetes, greater than 30–pack year history of smoking, postoperative ventricular dysfunction, and preoperative diuretic use, peak postoperative BNP no longer significantly predicted lower postoperative PCS score (effect estimate, −1.87; 95% CI, −3.95 to 0.21; $P = 0.08$). Preoperative PCS score was the strongest predictor of postoperative PCS score in the multivariable model ($P < 0.0001$). As with the PF score multivariable results, the age ≥65 yr by peak postoperative BNP interaction term was not significant ($P > 0.05$) when added into both the multivariable RP and PCS models.

Discussion

As CABG surgery is performed on progressively older patients, it is increasingly evident that patients undergo this surgery to improve postoperative functional status, as well as to avert potential mortality.[2,3] In fact, the American College of Cardiology/American Heart Association's guidelines for CABG surgery define the primary indications for CABG surgery as follows: to improve both postoperative quality of life and survival.[35] Although postoperative HRQL improves for most patients who undergo CABG surgery, up to approximately 25% have experienced postoperative deterioration in HRQL.[4–8] Identifying modifiable perioperative risk factors for decreased HRQL after CABG surgery could improve treatments and interventions to improve patients' postoperative functional status and associated morbidity and mortality. In the current study, increased peak postoperative BNP significantly predicts lower SF-36 PF domain scores, assessed

at 6 months, 1 yr, and 2 yr after isolated primary CABG surgery with CPB. This remained true even after adjusting for clinical predictors, including preoperative PF score and the development of significant postoperative ventricular dysfunction. The idea that increased postoperative BNP predicts lower postoperative PF is further strengthened by our secondary finding that increased peak postoperative BNP independently predicts lower postoperative RP domain scores. Increased in-hospital peak postoperative BNP has previously been identified as an independent predictor of all-cause mortality in patients undergoing primary CABG surgery[27] and of 1-yr major adverse cardiovascular events in patients undergoing CABG and valve surgery.[28] However, this variable was not previously assessed for its association with quality of life after CABG surgery.

Our findings that preoperative PF,[6,36] older age,[6] female sex,[8,37,38] obesity,[36] diabetes,[6,36,39] and smoking[6,36,39] are important clinical predictors of lower postoperative PF are consistent with previous studies of SF-36 questionnaire responses in CABG cohorts. However, although these clinical risk factors may be useful for pre-CABG counseling of patients regarding their likelihood of experiencing declines in HRQL, these risk factors are not readily modifiable. Smoking cessation should be routinely advocated, but much of the associated lung damage is likely permanent by the time patients undergo CABG surgery; obesity takes months of diet and exercise intervention to mitigate and is notoriously refractory to intervention. The primary novelty of our study is focused on the demonstration that both in-hospital postoperative ventricular dysfunction, defined clinically as the need for multiple inotropes or intraaortic balloon pump support, and increased peak postoperative BNP independently and significantly predict post-CABG decline in PF, even after adjusting for other demographic and clinical predictors.

Because studies[19–21] of patients who experienced ambulatory heart failure found that medical management, guided by serial follow-up BNP or N-terminal pro-BNP measures, is associated with improved heart failure readmission–free survival, it is conceivable that patients with increased peak postoperative BNP after CABG surgery may experience better PF outcomes with similar models of postoperative surveillance and treatment. One outpatient heart failure management study[21] reported an attenuated response to an N-terminal pro-BNP–guided intervention in elderly patients. However, our analysis indicated that age does not significantly alter the association between peak postoperative BNP and postoperative PF. In addition, participation in a postdischarge cardiac rehabilitation program has been associated with improved PF 1 yr after CABG surgery.[40] Similar interventions in patients who undergo CABG surgery and have an increased peak postoperative BNP could help prevent postoperative declines in PF.

When considered individually, both increased preoperative BNP and peak postoperative BNP are significantly associated with longer hospital stays and increased all-cause mortality up to 5 yr after primary CABG surgery, even after adjusting for important clinical risk factors.[27] An intriguing finding of that study was that when preoperative and peak postoperative BNP concentrations were entered together into the multivariable clinical model for predicting length of hospital stay, despite correlation between these two BNP measures, both were independent predictors of longer hospital length of stay. This suggests that the peak postoperative BNP concentration detects clinically relevant intraoperative and early postoperative cardiac insults that cannot be detected using preoperative BNP concentration alone. In the current study, increases in both preoperative and peak postoperative BNP were associated with lower post-CABG PF in univariate assessments, but the peak postoperative BNP association was more robust and was the only one to remain significant after multivariable adjustments.

Several potential limitations of our study deserve consideration. First, this study included patients undergoing nonemergency primary CABG-only surgery with CPB; therefore, the results cannot necessarily be extrapolated to higher-risk CABG surgery or valve surgery. However, because patients undergoing nonemergency isolated primary CABG surgery are possibly more motivated to undergo CABG surgery with the expectation of improving their longer-term functional status, we believe that our study hypothesis was addressed in a particularly relevant subset of cardiac surgical patients. Second, although the number of subjects missing preoperative or postoperative SF-36 PF domain score assessments in our study is consistent with previous studies[4,6,36,37] of post-CABG HRQL, as with previous studies, bias related to missing data cannot be excluded. In our study, most perioperative patient characteristics did not differ significantly between those subjects with and without missing PF assessments; institution of enrollment and minority status (the strongest predictors of subjects missing PF score data required for analysis) were adjusted for in all multivariable assessments of SF-36 postoperative functional status. Furthermore, sensitivity analysis results suggest that the independent association we report between increased peak postoperative BNP and lower postoperative PF scores is robust even if no association between increased peak postoperative BNP and postoperative PF scores is assumed for subjects excluded for missing follow-up PF scores. Third, as with any multiinstitution study, we may not be able to completely account for institutional variations in perioperative management. However, potential confounding related to institutional practice was statistically adjusted for by including institution as a covariate in the study's multivariable models. Finally, although the association observed between increased peak postoperative BNP concentration and lower SF-36 PF domain scores is significant, the effect size was modest after adjusting for other important clinical risk factors. Future studies may be warranted to assess the association between peak postoperative BNP concentration and other quality-of-

life related clinical outcomes, such as hospital readmissions for heart failure.

In conclusion, in this study of patients undergoing primary CABG surgery, increased peak postoperative BNP concentrations predict significantly lower SF-36 PF assessments conducted up to 2 yr after surgery. Early identification of cardiac surgical patients at risk of having lower postoperative PF provides an opportunity to initiate prompt postoperative interventions, such as enrollment in cardiac rehabilitation programs, aggressive titration of medications (*e.g.*, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers), and other measures directed toward mitigating declines in postoperative HRQL. Future studies are needed to determine whether BNP guidance of such interventions can improve PF and other HRQL measures after CABG surgery.

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