Published in final edited form as:
Anesthesiology. 2011 April ; 114(4): 807–816. doi:10.1097/ALN.0b013e31820ef9c1.

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

Amanda A. Fox, MD, MPH[*,^], **Edward R. Marcantonio, MD, SM**[#,±], **Charles D. Collard, MD**[@,¶], **Mathis Thoma, PhD**[§,†], **Tjorvi E. Perry, MD, MMSc**[*,^], **Stanton K. Shernan, MD**[*,±], **Jochen D. Muehlschlegel, MD, MMSc**[*,^], and **Simon C. Body, MBChB, MPH**[±,*]

[*] Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA

[#] Division of General Medicine and Primary Care, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02115, USA

[¶] Baylor College of Medicine Division of Cardiovascular Anesthesia at the Texas Heart Institute, Saint Luke's Episcopal Hospital, Houston, TX 77225, USA

[§] Department of Biostatistics, Harvard School of Public Health, Boston, MA 02115, USA

Abstract

Background—Elevated 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 elevated postoperative BNP predicts worse post-discharge physical function (PF) is unknown. We hypothesized that peak postoperative BNP associates with PF assessed up to 2 years 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 and 2 years 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 years after CABG surgery, multivariable longitudinal regression analysis of the postoperative PF scores was performed, adjusting for important clinical risk factors.

Results—845 subjects (mean age±SD: 65±10 years) 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, −5.64; P=<0.0001). After multivariable adjustments, peak

Corresponding Author: Amanda A. Fox, MD, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA, Telephone: 617-732-8222, Fax: 617-732-6798, afox@partners.org.
[+]Instructor
[^]Assistant Professor
[±]Associate Professor
[@]Professor
[†]Research Associate

Department and Institution to which the work should be attributed: Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, MA

Presented at the American Society of Anesthesiologists' 2010 Annual Meeting, San Diego, CA, Oral Discussion, October 19th, 2010

postoperative BNP remained independently associated with postoperative PF (effect estimate for $\log_{10}$ peak BNP =−3.06 PF score points; 95% CI = −5.15, −0.97; P=0.004).

Conclusions—Elevated peak postoperative BNP independently associates with worse longer-term physical function after primary CABG surgery. Future studies are needed to determine whether medical management targeted towards reducing elevated postoperative BNP can improve PF after CABG surgery.

INTRODUCTION

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 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] While for the majority of patients undergoing CABG surgery, postoperative HRQL improves or at least remains the same as before surgery, 7–24% of CABG patients 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 towards improving postoperative functional status, as well as 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 ambulatory heart failure and acute coronary syndrome patients.[10–18] Several studies of BNP (or N-terminal proBNP) guided chronic heart failure treatment interventions suggest corresponding reductions in adverse cardiac events.[19–22] In the setting of CABG surgery, elevated 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 elevated postoperative BNP predicts significant declines in physical function during the first several years after CABG surgery is unknown.

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

MATERIALS AND METHODS

Study Population

Between August 2001 and September 2006, 1,519 men and women aged 20 to 89 years scheduled for isolated primary CABG surgery with CPB at Brigham and Women's Hospital, Boston, MA and Texas Heart Institute, St. Luke's Episcopal Hospital, Houston, TX were enrolled prospectively into an ongoing study known as the *CABG Genomics Program*.* Institutional Review Board approvals (Partners Institutional Review Board, Boston, MA, USA and St. Luke's Episcopal Hospital Institutional Review Board, Houston, TX, USA) and subject written informed consent were obtained. *CABG Genomics Program* exclusion

*http://clinicaltrials.gov/show/NCT00281164, last updated July 10th, 2009

criteria include a preoperative hematocrit <25% or transfusion of leukocyte-rich blood products within 30 days before surgery. Enrolled subjects were additionally prospectively excluded from analysis for this study if they had undergone prior cardiac surgery, if they underwent emergency surgery or concurrent valve surgery, if they received a preoperative inotrope, intra-aortic 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 preoperative serum creatinine > 3 mg/dL) were excluded from analysis because severe renal dysfunction and perioperative dialysis can variably affect perioperative plasma BNP concentrations.[29,30] Subjects were additionally 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, co-morbidities and medications, surgical characteristics, and postoperative in-hospital events were collected for each enrolled subject during their primary hospitalization using a detailed case report form. Postoperative patient survival was assessed by mail and telephone interviews and by examinations of the Social Security Death Index through May, 2009. Plasma samples were obtained preoperatively and on postoperative days (POD) 1–5, and were stored in vapor-phase liquid nitrogen until analysis. BNP and cardiac troponin I 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 at the time of patient care.

HRQL assessments were conducted preoperatively and 6 months, 1 and 2 years after surgery using the SF-36 Health Survey questionnaire (SF-36v2®; version 2, acute 1 week recall).[31] To avoid confounding the assessment of perioperative predictors of longer-term postoperative PF by other significant postoperative life factors that could influence physical function (e.g., advancing age), we limited our analysis to 2 years 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 the SF-36 scoring (1998 United States population adjusted normative scores with population mean score = 50, and a 10 point score change representing one standard deviation).[31]

The SF-36 questionnaire is a validated HRQL assessment instrument that evaluates eight health domains: physical function (PF; 10 questions), role physical (RP; 4 questions), as well as bodily pain, general health, vitality, social functioning, role emotional, and mental health. 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. RP domain questions assess how physical health limits ability to accomplish work related or other usual activities. The physical (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 biology underlying elevated BNP (i.e., distressed myocardium) is likely to associate most with decreased PF. RP domain and PCS scores were

also identified prospectively as secondary outcomes because these assessments should also reflect aspects of postoperative physical function. We chose the time period extending from 6 months to 2 years after surgery to represent physical function after recovery from CABG surgery and employed methods for analysis of repeated measurements to estimate a constant association between peak postoperative BNP and physical function during this time 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 levels tend to rise significantly during PODs 1–3 and then plateau between 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 level of BNP during the first 5 PODs.

Postoperative creatinine clearance was estimated using the highest of the routine postoperative creatinine measures made during primary hospitalization. Postoperative ventricular dysfunction was defined as a new requirement for 2 or more inotropes or new placement of an intra-aortic 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 (> 5μg/kg/min), epinephrine, isoproterenol, norepinephrine or vasopressin.

Statistical Analyses

Statistical analyses were performed using R (R version 2.11.1, 2010-05-31; R Foundation for Statistical Computing, Vienna, Austria). Mean baseline, 6 month, 1 and 2 year PF domain scores were compared between pairs of time-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 chi-square, Fisher's Exact or Wilcoxon rank sum tests as appropriate. P value assessments for all study analyses were two-tailed.

SF-36 domain and component summary scores assessed 6 months, 1 and 2 years 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 time points are not statistically independent. Model parameters were estimated by the method of restricted maximum likelihood estimation. We assumed that the association between peak postoperative BNP and physical function remained constant during the 6 month to 2 year postoperative time period; the coefficient of $\log_{10}$ peak postoperative BNP in our models estimates this constant association. Since continuous plasma BNP and cardiac troponin I values were right skewed, these variables were $\log_{10}$ transformed prior to 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 years), gender, 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 confidence interval 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. BIC is more conservative than the other commonly used criterion, the Akaike Information Criterion for adding variables to a multivariable model. To avoid model overfitting we therefore used BIC instead of the Akaike Information Criterion to select variables for inclusion in the final multivariable prediction model.

Though they dropped out of the multivariable model during stepwise selection, preoperative left ventricular ejection fraction, peak postoperative cTnI, and postoperative creatinine clearance covariates were individually 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, and these variables were therefore not included in the final multivariable prediction model. We did not adjust for time point of follow-up questionnaire assessment within our repeated measures regression model because this did not significantly improve model fit when compared with the simpler regression model that assumed a constant association between peak postoperative BNP and physical function scores during the 6 month to 2 year postoperative time period.

We repeated the multivariable modeling approaches described for the postoperative PF outcome to assess whether peak postoperative BNP also independently predicts the secondary RP domain and PCS score outcomes. To assesses potential effect modification of the association between peak postoperative BNP and longitudinal SF-36 outcomes by age, we added an age ≥65 years 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 3 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 and 2 year 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. 100 postoperative PF score datasets were created for each of the six hypothetical regression coefficient values, and regression coefficients and corresponding standard errors for $\log_{10}$ peak postoperative BNP were then estimated for each of the six scenarios by the method of 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, loss to follow-up and available perioperative PF domain scores. As reported previously, of the 1,519 subjects enrolled into the *CABG Genomics Program* during the study period, 336 subjects 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 subjects (78.2%) provided PF domain scores for 6 months, 1 year, or 2 year 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 6 month follow-up.

When compared with the analyzed subjects, patients excluded for missing PF score data were significantly ($P<0.05$) younger (61±10 years; mean and SD), had higher preoperative creatinine clearance (77±24 mL/min/1.73m^2), and were more likely to be minorities (28.4%), to have a body mass index >30 kg/m^2 (44.7%), to undergo >120 minutes of CPB (16.9%), to have received a preoperative non-aspirin platelet inhibitor (27.5%), or to have not received a preoperative beta blocker (28.1%). The group missing PF scores also developed significantly less postoperative atrial fibrillation (23.7%), were more frequently enrolled at one of the study institutions (45.3%), and had lower preoperative (41.9±86.0 pg/mL) and peak postoperative BNP measures (211.9±192.3 pg/mL). 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 Physical Function Domain Scores

As shown in Figure 2, postoperative 6 month, 1 year, and 2 year PF domain scores were significantly improved when compared with preoperative PF domain scores ($P<0.0001$). PF domain scores did not differ significantly between 6 months and 1 year 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 Physical Function

Demographic, medical, and surgical characteristics of the analyzed study subjects are shown in Table 1 along with each characteristic's univariate association with postoperative PF domain scores. The mean and SD of the age of this subject group was 65±10 years. Subject characteristics with the strongest univariate associations with postoperative PF domain scores were preoperative PF domain score, postoperative ventricular dysfunction, female gender, and preoperative age ≥65 years.

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

Median peak postoperative BNP concentration was 191.3 pg/mL, with an interquartile range of 120.1–319.2 pg/mL. Mean and SD peak postoperative BNP was 260.3 ± 241.5 pg/mL. Univariate assessment of associations between peak postoperative BNP and the ten SF-36 postoperative outcome scores are shown in Table 3. As we hypothesized, elevated peak postoperative BNP was strongly associated with postoperative PF domain score (effect estimate = −7.66, 95% CI: −9.68, −5.64; $P<0.0001$) and was also strongly associated with postoperative RP domain (effect estimate= −5.38, 95% CI: −7.34, −3.42; $P<0.0001$) and PCS (effect estimate= −6.19, 95% CI: −8.17, −4.22) scores. Peak postoperative BNP was

not associated with the postoperative mental health domain or mental health summary score (P>0.05).

Multivariable Adjusted Association between Peak Postoperative BNP and Postoperative Physical Function Domain Scores

We further assessed the value of peak postoperative BNP concentration for predicting postoperative PF scores after adjusting for demographic characteristics (age ≥65 years, gender, institution and minority status) and other clinical predictors including preoperative PF score, obesity (body mass index >30kg/m^2), >30 pack year history of smoking, occurrence of postoperative ventricular dysfunction, diabetes, and preoperative diuretic use (Table 2). Even after multivariable adjustments, elevated peak postoperative BNP predicts lower postoperative PF scores (effect estimate = −3.06; 95% CI: −5.15, −0.97; P=0.004). When we added an age ≥65 years 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 elevated peak postoperative BNP and lower postoperative PF. 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 year postoperative PF scores (regression coefficient = 0.00), the overall association between elevated 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 Physical Component Summary Scores

Elevated peak postoperative BNP also remained a significant predictor of lower postoperative RP domain scores after adjusting for demographic characteristics (age ≥65 years, gender, institution and minority status) and other clinical predictors including preoperative RP domain score, obesity (body mass index >30kg/m^2), myocardial infarction within 2 weeks of surgery, >30 pack year history of smoking, and preoperative diuretic use (effect estimate= −2.72; 95% CI: −4.93, −0.52; P=0.02). After adjusting for demographic characteristics and other clinical predictors including preoperative PCS domain score, obesity (body mass index >30kg/m^2), diabetes, >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, 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, age ≥65 years by peak postoperative BNP interaction terms were not significant (P>0.05) when added into 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 to be to improve both postoperative quality of life and survival.[35] While postoperative HRQL improves for the majority of CABG patients, up to ~25% have been reported to experience 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, as well as associated morbidity and mortality. In the present study, elevated peak postoperative BNP significantly predicts lower SF-36 PF domain scores assessed at 6 months, 1 and 2 years

after isolated primary CABG surgery with CPB. This remained true even after adjusting for clinical predictors including preoperative PF score and development of significant postoperative ventricular dysfunction. That elevated postoperative BNP predicts lower postoperative physical function is further strengthened by our secondary finding that increased peak postoperative BNP also independently predicts lower postoperative RP domain scores. Elevated in-hospital peak postoperative BNP has previously been identified as an independent predictor of all-cause mortality in primary CABG patients[27] and of 1 year major adverse cardiovascular events in CABG and valve surgical patients,[28] but it had not been assessed previously for its association with quality of life after CABG surgery.

Our findings that preoperative physical function,[6,36] older age,[6] female gender,[8,37,38] obesity,[36] diabetes,[6,36,39] and smoking[6,36,39] are important clinical predictors of lower postoperative physical function are consistent with prior studies of SF-36 questionnaire responses in CABG cohorts. However, while 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, and 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 need for multiple inotropes or intra-aortic balloon pump support and elevated peak postoperative BNP independently and significantly predict post-CABG decline in physical function, even after adjusting for other demographic and clinical predictors.

Since studies of ambulatory heart failure patients have found that medical management guided by serial follow-up BNP or N-terminal proBNP measures is associated with improved heart failure readmission free survival,[19–21] it is conceivable that CABG patients with elevated peak postoperative BNP may have better physical function outcomes with similar models of postoperative surveillance. One outpatient heart failure management study reported an attenuated response to N-terminal proBNP guided intervention in elderly patients.[21] However, our analysis indicated that age does not significantly alter the association between peak postoperative BNP and postoperative physical function. Also intriguing is that participation in a post-discharge cardiac rehabilitation program has been associated with improved physical function 1 year after CABG surgery. [40] It could be speculated that similar interventions in CABG patients with elevated peak postoperative BNP could help prevent postoperative declines in physical function.

We have previously reported that when considered individually, both elevated preoperative BNP and peak postoperative BNP are significantly associated with longer hospital stays and increased all-cause mortality up to 5 years 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 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 peak postoperative BNP is detecting clinically relevant intraoperative and early postoperative cardiac insults that cannot be detected using preoperative BNP alone. In the present study it is important to note that elevations in both preoperative and peak postoperative BNP were associated with lower post-CABG physical function 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 non-emergency primary CABG-only surgery with CPB, so results cannot necessarily be extrapolated to higher-risk CABG surgery or valve surgery. However, since it is patients undergoing non-emergency isolated primary CABG surgery who 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, while the number of subjects missing preoperative or postoperative SF-36 PF domain score assessments in our study is consistent with prior studies of post-CABG HRQL, as with prior studies, bias related to missing data cannot be ruled out.[4,6,36,37] In our study the majority of perioperative patient characteristics did not differ significantly between those subjects with and without missing PF assessments, and 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 elevated peak postoperative BNP and lower postoperative PF scores is robust even if no association between elevated peak postoperative BNP and postoperative PF scores is assumed for subjects excluded for missing follow-up PF scores. Third, as with any multi-institution 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, while the association observed between elevated peak postoperative BNP 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 and other quality of life related clinical outcomes such as hospital readmissions for heart failure.

CONCLUSIONS

In this study of primary CABG surgery patients, elevated peak postoperative BNP concentrations predict significantly lower SF-36 PF assessments conducted up to 2 years following 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 such as angiotensin converting enzyme-inhibitors, angiotensin receptor blockers, and beta-blockers, as well as other measures directed towards mitigating declines in postoperative HRQL. Future studies are needed to determine if BNP guidance of such interventions can improve PF and other HRQL measures after CABG surgery.

Acknowledgments

We thank Professor James Ware, Ph.D.[§ @] for his expert and invaluable statistical consultations regarding the design and conduct of the statistical analyses for this manuscript, and we also thank Kuang-Yu Liu, Ph.D.[*+] for his suggestions regarding our approach to multivariable regression model building. We want to acknowledge the outstanding contributory efforts of the CABG Genomics Program's research staff: Kutjim Bodinaku, MD (Research Assistant*), Svetlana Gorbatov, MPH (Research Assistant*), James Gosnell, RN (Research Nurse*), Sejfudin Kavazovic, CRA (Research Assistant[¶]), Adrienne Kicza, BS (Research Assistant*), and Charles Wellington, RN, BSN, CCRC (Research Nurse[¶]). Finally we thank all the individuals who have participated in the coronary artery bypass graft (CABG) Genomics Program.

Funding: Biosite Incorporated, San Diego**,** C**a**lifornia; Harvard Clinical and Translational Science Center, from the National Center for Research Resources (UL1 RR025758-01); Foundation for Anesthesia Education and Research Starter Grant**,** Rochester, Minnesota (Principal Investigator: A. A. Fox); Dennis W. Jahnigen Career Development Scholars Award, American Geriatrics Society, New York, New York (Principal Investigator: A. A. Fox); N**a**tional Institute of Health grant, Bethesda, Maryland (K23HL068774 and RO1HL098601; Principal Investigator: S. C. Body); Funding from the Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's

Hospital**,** Boston, Massachusetts and Baylor College of Medicine Division of Cardiovascular Anesthesia at the Texas Heart Institute, Saint Luke's Episcopal Hospital, Houston, Texas

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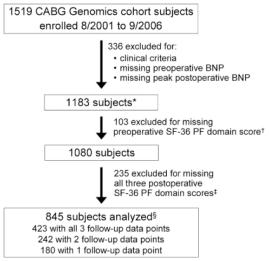

Figure 1.

This diagram outlines subject exclusions from the CABG Genomics Program cohort for this study.

* A total of 47 of the 1,183 subjects eligible for analysis died during the 2-yr study follow-up period (4%). 17 of these subjects died before 6 month follow-up.

†Of the 103 subjects excluded for missing preoperative PF score data, 3 subjects died before 6 month follow-up, and 2 subjects died between 1 and 2 yr follow-up

‡Of the 235 subjects additionally excluded for having no follow-up postoperative PF score follow-up, 14 subjects died before 6 month follow-up, 9 subjects died between 6 months and 1 yr follow-up, and 5 subjects died between 1 and 2 yr follow-up.

§Of the 845 analyzed subjects, 2 subjects died between 6 months and 1 yr follow-up, and 12 subjects died between 1 and 2 yr follow-up.

BNP = B-type natriuretic peptide; CABG = coronary artery bypass graft; PF = physical function; SF = Short Form

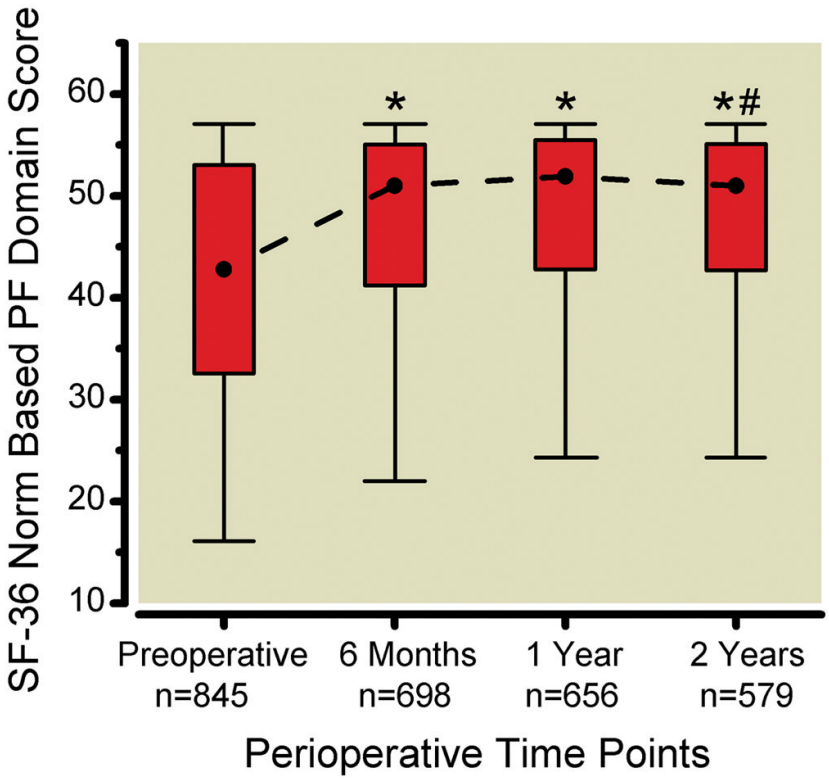

Figure 2.

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 time points

*signifies significantly higher than preoperative baseline ($P < 0.0001$). # signifies significantly lower than prior postoperative time point ($P = 0.0001$).

PF = physical function; SF = Short Form

Table 1

Univariate associations between perioperative clinical risk factors and postoperative SF-36 questionnaire physical function domain scores assessed 6 months through 2 years after primary coronary artery bypass graft surgery.*

Predictor Variables (n=845)	Mean or Proportion	Effect Estimate (95% CI)	P value
Demographics and Preoperative Risk Factors			
Age ≥ 65 years	420 (49.7%)	−4.07 (−5.31. −2.82)	<0.0001
Female gender	163 (19.3%)	−5.26 (−6.84, −3.68)	<0.0001
Institution			
Brigham and Women's Hospital	694 (82.1%)		
Texas Heart Institute	151 (17.9%)	0.37 (−1.30, 2.05)	0.66
Ethnicity (minority)	94 (11.1%)	−1.42 (−3.47, 0.62)	0.17
Preoperative SF-36 physical function domain score*	42.1 ± 11.5	0.36 (0.31, 0.41)	<0.0001
Diabetes mellitus (n=844)	238 (28.2%)	−3.51 (−4.91, −2.11)	<0.0001
Hypertension (n=843)	628 (74.3%)	−1.89 (−3.36, −0.43)	0.01
Hypercholesterolemia (n=841)	642 (76.0%)	1.02 (−0.49, 2.53)	0.19
Obesity (BMI >30 kg/m^2)	320 (37.9%)	−3.43 (−4.73, −2.13)	<0.0001
Smoking, >30 pack year history (n=816)	224 (26.5%)	−3.37 (−4.81, −1.93)	<0.0001
Preoperative creatinine clearance (mL/min/1.73m^2)	74 ± 19	0.06 (0.02, 0.09)	0.0008
Myocardial infarction ≤2 weeks preoperatively (n=844)	149 (17.6%)	−2.00 (−3.69, −0.32)	0.02
Left ventricular ejection fraction (%) (n=816)	53 ± 12	0.10 (0.05, 0.15)	0.0001
Coronary artery regions with >50% stenosis			
0–1 region	53 (6.3%)	--	--
2 regions	281 (33.3%)	0.53 (−2.26, 3.32)	0.71
3 regions	511 (60.5%)	1.19 (−1.50, 3.88)	0.39
Mitral insufficiency (moderate or severe; n=819)	16 (1.9%)	−5.78 (−10.49, −1.06)	0.02
Past arrhythmia	83 (9.8%)	−1.92 (−4.06, 0.23)	0.08
Anemia	288 (34.1%)	−3.59 (−4.92, −2.27)	<0.0001
Preoperative BNP (pg/mL)	17.6 [4.9, 50.4]	−1.89 (−2.51, −1.26) for $\log_{10}$ increase	<0.0001
Preoperative cTnI >0.1μg/L	127 (15.0%)	−1.78 (−3.57, 0.004)	0.05
Preoperative Medications			
ACE-inhibitor (n=844)	388 (45.9%)	−0.03 (−1.31, 1.26)	0.97

Predictor Variables (n=845)	Mean or Proportion	Effect Estimate (95% CI)	P value
Diuretic	178 (21.1%)	−3.73 (−5.28, −2.18)	<0.0001
Statin	659 (78.0%)	0.75 (−0.78, 2.29)	0.34
Digoxin	24 (2.8%)	−5.08 (−8.93, −1.22)	0.01
Beta blocker	670 (79.3%)	0.78 (−0.80, 2.36)	0.33
Calcium channel blocker	114 (13.5%)	−3.14 (−4.99, −1.29)	0.0009
Aspirin	651 (77.0%)	0.61 (−0.91, 2.13)	0.43
Non-aspirin platelet inhibitor	164 (19.4%)	−2.09 (−3.71, −0.48)	0.01
Nitroglycerin intravenous (n=842)	89 (10.5%)	−0.46 (−2.55, 1.63)	0.67
Heparin intravenous	199 (23.6%)	−0.59 (−2.09, 0.92)	0.44
Surgical Risk Factors			
Urgent surgery	466 (55.1%)	−1.56 (−2.84, −0.28)	0.02
Cardiopulmonary bypass time >120 minutes	200 (23.7%)	1.05 (−0.46, 2.55)	0.17
Number of coronary grafts (n=844)			
<3 grafts	122 (14.4%)	--	--
3 grafts	390 (46.2%)	−0.03 (−1.95, 1.89)	0.97
>3 grafts	332 (39.3%)	1.73 (−0.23, 3.69)	0.08
In-hospital postoperative outcomes			
Ventricular dysfunction	94 (11.1%)	−5.48 (−7.49, −3.47)	<0.0001
New onset atrial fibrillation	260 (30.8%)	−1.35 (−2.74, 0.03)	0.05
Postoperative creatinine clearance (mL/min/1.73m^2; n=844)	68 ± 21	0.09 (0.06, 0.12)	<0.0001
Peak postoperative cTnI (μg/L)	1.34 [0.66, 2.84]	−1.91 (−3.09, −0.73) for $\log_{10}$ increase	0.002

Data are shown as n (%) for dichotomous variables and mean ± standard deviation or median [25th, 75th percentiles] for continuous variables.

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

* SF-36 questionnaire physical function domain score is a normative based score derived by SF-36 version 2 acute 1 week recall scoring algorithm based on 1998 United States population adjusted normative scores (population mean score = 50, with a 10 point change in score representing one standard deviation). Postoperative SF-36 physical function domain scores were assessed at 6 months, 1 and 2 years after CABG surgery.

Table 2

Multivariable longitudinal regression model for predicting SF-36 physical function domain scores assessed 6 months through 2 years after primary coronary artery bypass graft surgery

n = 815*	**Model *including* Log_{10} Peak Postoperative BNP BIC = 12661.90**		**Model *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, −0.97)**	**0.004**	–	–
Preoperative SF-36 physical function domain score	0.26 (0.21, 0.31)	<0.0001	0.27 (0.22, 0.32)	<0.0001
Age ≥ 65 years	−3.21 (−4.39, −2.03)	<0.0001	−3.62 (−4.77, −2.47)	<0.0001
Gender (Female)	−2.17 (−3.63, −0.70)	0.004	−2.55 (−4.00, −1.11)	0.0006
Institution	−1.05 (−2.62, 0.51)	0.19	−0.64 (−2.19, 0.91)	0.42
Minority	−1.78 (−3.58, 0.03)	0.05	−1.73 (−3.54, 0.09)	0.06
Obesity (BMI > 30 kg/ m^2)	−2.60 (−3.79, −1.41)	<0.0001	−2.36 (−3.55, −1.18)	0.0001
Diabetes	−1.78 (−3.03, −0.53)	0.005	−1.92 (−3.17, −0.67)	0.003
Smoking (>30 pack year history)	−2.21 (−3.48, −0.93)	0.0007	−2.41 (−3.68, −1.14)	0.0002
Preoperative diuretic	−1.60 (−2.99, −0.21)	0.02	−1.81 (−3.20, −0.42)	0.01
Postoperative ventricular dysfunction	−2.79 (−4.65, −0.94)	0.003	−3.43 (−5.24, −1.62)	0.0002

*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; SF = Short Form

Table 3

Univariate associations between $\log_{10}$ peak postoperative BNP and SF-36 domain and component summary scores assessed 6 months through 2 years after primary coronary artery bypass graft surgery.*

SF-36 Scores	Mean Score ± SD†	Effect Estimate (95% CI)‡	P value
Physical function domain score (n=845)	47.5 ± 9.6	−7.66 (−9.68, −5.64)	<0.0001
Role physical domain score (n=837)	48.6 ± 9.2	−5.38 (−7.34, −3.42)	<0.0001
Bodily pain domain score (n=842)	52.8 ± 8.9	−2.72 (−4.63, −0.81)	0.005
General health domain score (n=844)	49.7 ± 9.1	−2.86 (−4.84, −0.88)	0.005
Vitality domain score (n=842)	53.1 ± 9.0	−3.73 (−5.70, −1.77)	0.0002
Social functioning domain score (n=843)	51.5 ± 7.4	−1.66 (−3.23, −0.09)	0.04
Role emotional domain score (n=836)	49.4 ± 8.5	−3.36 (−5.17, −1.55)	0.0003
Mental health domain score (n=842)	52.2 ± 8.5	−0.76 (−2.63, 1.10)	0.42
Physical component summary score (n=837)	49.0 ± 9.2	−6.19 (−8.17, −4.22)	<0.0001
Mental component summary score (n=837)	52.5 ± 8.3	−0.08 (−1.90, 1.73)	0.93

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

*Scores and associations were assessed using data from the 845 subjects who had 6 month, 1, or 2 year physical function domain scores.

The 8 SF-36 domain scores are normative based scores derived using the SF-36 (version 2) acute 1 week recall scoring algorithm based on 1998 United States population adjusted normative scores (population mean score = 50, with a 10 point change in score representing one standard deviation). Component summary scores are derived for subjects with at least 7 of the 8 domain scores using principal component analyses implemented by the SF-36 version 2 acute 1 week recall scoring algorithm.

†Mean of available 6 month, 1 and 2 year scores

‡Effect estimates and P values derived from longitudinal regression analysis of postoperative 6 month, 1 year and 2 year data.