

Utility of B-Type Natriuretic Peptide in Predicting Postoperative Complications and Outcomes in Patients Undergoing Heart Surgery

Ryan Hutfless, MD,† Radmila Kazanegra, MD,* Michael Madani, MD,*† Meenakshi Awasthi Bhalla, MD,‡ Alisi Tulua-Tata, BS,† Amelia Chen, BS,† Paul Clopton, MS,* Cherimarie James, RN,* Albert Chiu, BS,* Alan S. Maisel, MD*†

San Diego, California; and Buffalo, New York

OBJECTIVES	The purpose of the present study was to assess whether preoperative and postoperative B-type natriuretic peptide (BNP) levels could be used as predictors of postoperative complications and outcomes in patients after open-heart surgery.
BACKGROUND	A variety of multifactor indexes have been proposed for preoperative risk assessment of patients undergoing cardiac surgery, but they have shown limited ability and utility in accurately predicting postoperative complications, hospital stay, and mortality.
METHODS	Subjects consisted of 98 male patients (63 ± 9.1 years) undergoing open-heart surgery at the San Diego Veterans Administration Health System during a 19-month period. B-type natriuretic peptide levels were analyzed, and postoperative data recorded.
RESULTS	There was a higher preoperative BNP level in patients requiring the use of intra-aortic balloon pumps (IABPs) (mean BNP = 387 ± 112 pg/ml vs. 181 ± 25 pg/ml), in patients who died within one year (357 ± 93 pg/ml vs. 184 ± 26 pg/ml), and in patients with postoperative hospital stays of 10 days or more (307 ± 68 pg/ml vs. 179 ± 27 pg/ml). Receiver operating characteristic curves demonstrated preoperative BNP levels as predictors of postoperative IABP use, hospital stay ≤ 10 days, and mortality < 1 year with areas under the curve of 0.70, 0.64, and 0.70, respectively. A BNP cut-off value above 385 pg/ml demonstrated high specificity ($= 90\%$ in each) and accuracy ($= 86\%, 79\%, 85\%$, respectively) for predicting each of these end points.
CONCLUSIONS	Preoperative BNP levels > 385 pg/ml predict the postoperative complications and one-year mortality after heart surgery. Postoperatively, elevated peak BNP levels and elevated change to peak BNP levels were associated with prolonged hospital stay and mortality within one year. (J Am Coll Cardiol 2004;43:1873–9) © 2004 by the American College of Cardiology Foundation

Open-heart surgery is associated with significant risk for postoperative cardiac events. A variety of multifactorial risk indexes have been described to help delineate preoperative risk assessment of patients undergoing cardiac surgery (1–5). However, their ability to effectively predict postoperative complications, hospital stay, and mortality is uncertain, and no gold standard currently exists (6,7). Furthermore, many of these assessment tools are not routinely utilized in preoperative evaluation because of complexity, inaccuracy when applied to individuals, unavailability of important variables, and/or time constraints (6,8,9). Some of these indexes also rely on the clinical judgment of evaluating physicians, introducing potential for wide variation based on experience and competency (5). A valuable addition to the preoperative evaluation would be a quanti-

tative, cost-effective, time-efficient serum marker capable of accurately predicting postoperative length of hospital stay, morbidity, and mortality.

B-type natriuretic peptide (BNP) is a cardiac hormone that is synthesized by ventricular myocytes in response to ventricular dysfunction and wall-stress (10). It modulates plasma volume and myocardial stretch through its actions as a diuretic, a renin-angiotensin-aldosterone system antagonist, and as an inhibitor of sympathetic outflow and vasoconstrictor production (11). Recent studies have demonstrated the utility for BNP levels in recognizing and predicting congestive heart failure (HF) exacerbations in patients presenting to the emergency department with dyspnea (12,13).

It has previously been demonstrated that, after heart surgery, BNP correlates with a marker for myocardial ischemia, creatine kinase-MB (14), as well as with recovery of ventricular function (15). Most of the multivariable risk indexes for preoperative assessment use ejection fraction as a major factor in their calculations of risk, and studies have shown that low ejection fraction alone is one of the best independent predictors of postoperative morbidity and mor-

From the *Department of Medicine, Division of Cardiology, Department of Surgery, San Diego VA Healthcare System, San Diego, California; †University of California, San Diego, San Diego, California; and the ‡University of Buffalo, Mercy Hospital, Buffalo, New York. Dr. Maisel is a consultant for Biosite, Inc. Dr. Kazanegra receives salary support from Biosite, Inc. Dr. Jagat Narula acted as Guest Editor for this manuscript.

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Abbreviations and Acronyms

AUC	= area under the curve
BNP	= B-type natriuretic peptide
HF	= heart failure
IABP	= intra-aortic balloon pump
ROC	= receiver operating characteristic

tality (16). Therefore, it seems logical that preoperative BNP could be capable of predicting postoperative outcomes because it has been shown to correlate with ejection fraction and ventricular dysfunction (17,18).

The purpose of the present study was to assess whether preoperative and postoperative BNP levels could be used as predictors of postoperative complications and outcomes in patients after open-heart surgery. We hypothesized that patients with high pre- and postoperative BNP levels would encounter postoperative complications, prolonged hospital stay, readmission, and mortality. Likewise, we postulated that a quantitative level of BNP exists above which these adverse clinical end points are likely to occur.

METHODS

During the 19-month period (July 2000 to February 2002), we prospectively recruited 98 male patients, referred to the San Diego Veterans Affairs Health Care System for open-heart surgery, in compliance with the Human Research Protection Program at the University of California, San Diego. All male patients undergoing heart surgery at the VA hospital were eligible for inclusion, and every effort was made to recruit them in consecutive order. Female patients were excluded because they comprise an insignificant fraction of the VA patient population.

Study protocol. Patient records were evaluated before knowledge of BNP values. Past medical and surgical histories were determined by review of previous records. Echocardiogram and cardiac catheterization data were reported as by the attending cardiologist. Procedure and intraoperative data were determined by review of finalized surgical note and anesthesia record. Cardiac events and clinical end points were reported only after review and confirmation by an attending physician.

Blood samples (5 ml) were obtained from patients preoperatively and daily every morning postoperatively until the patient was discharged from the hospital. Blood was collected into a tube containing potassium EDTA. Samples were analyzed for BNP levels using a fluorescence immunoassay kit (Biosite Diagnostics, San Diego, California). The precision and sensitivity of this kit have been previously described (19).

Outcome data. Clinical end points included: 1) intraoperative and postoperative cardiac events: significant ST-segment change, significant arrhythmia, new Q-wave, or cardiac enzyme elevation; 2) ventilator dependence >48 h postoperatively; 3) intensive care unit stay longer than 5

Table 1. Patient Characteristics

Patient Data	
Total number of patients	98
Age (yrs)	63 ± 9.1
Preoperative ejection fraction (%)	55 ± 13
Myocardial infarction within 6 weeks preoperatively (patients)	7
CHF NYHA functional class III or IV (patients)	9
Insulin-dependent diabetes mellitus (patients)	10
Past cerebrovascular accident (patients)	10
Chronic renal insufficiency (patients)	7
Previous percutaneous transluminal coronary angioplasty/stent (patients)	19
Previous thoracotomy (patients)	9

Procedures	Number of Patients
CABG	84
Aortic valve replacement	19
Mitral valve replacement	4
Dual procedure (CABG + valve)	7
ASD repair	1
VSD repair	1
Re-do sternotomy	9

ASD = atrial septal defect; CABG = coronary artery bypass grafting; CHF = congestive heart failure; NYHA = New York Heart Association; VSD = ventricular septal defect.

days postoperatively; 4) hospital stay longer than 10 days postoperatively; 5) emergency reintubation other than for reoperation; 6) cardiothoracic reoperation within 2 weeks of initial surgery; 7) readmission within 30 days for cardiac reasons; 8) requirement for intra-aortic balloon pump (IABP); 9) mortality within 30 days and within 1 year postoperatively; and 10) postoperative requirement for epinephrine, lidocaine, and/or pressor doses of dopamine.

Statistical analysis. Correlations of preoperative BNP values with other variables were made using Pearson's correlation. Mean BNP values among groups were compared using the Student *t* test. Median postoperative BNP levels were compared using nonparametric Mann-Whitney test. All comparisons were calculated using log-transformed BNP concentrations to correct for known intrinsic skew in distribution. The utility of BNP as a prognostic indicator of intraoperative and postoperative complications was evaluated using receiver operating characteristic (ROC) curves. Preoperative ejection fraction, as determined by echocardiogram or cardiac catheter ventriculography, was also evaluated for its ability to predict intra- and postoperative complications using ROC curves.

RESULTS

The most relevant clinical information for the 98 patients is shown in Table 1. The mean patient age was 63 ± 9 years. The mean preoperative ejection fraction was 55%. Nine patients had New York Heart Association functional class III or IV symptoms on admission. Seven patients had a myocardial infarction within six weeks before surgery. Nine patients had previous thoracotomies. The majority of pa-

Table 2. Clinical End Points

Intra/Postoperative Data	Mean ± SD
Number of grafts	2.3 ± 1.3
Bypass time (min)	133 ± 39
Cross-clamp time (min)	83 ± 26
Dopamine >3 µg/kg/min (patients)	46
Epinephrine (patients)	26
Lidocaine (patients)	7
Postoperative hospital stay (days)	8.7 ± 11
Cardiac Events (n = 32)	Number of Patients
Intraoperative ST-segment change	4
Intraoperative arrhythmia	4
Postoperative new Q-wave	1
Postoperative ST-segment change	8
Postoperative arrhythmia	18
Postoperative cardiac enzyme elevation	3
Clinical End Points	Number of Patients
ICU >5 days postoperatively	11
Ventilator >2 days	13
Reintubation (not for surgery)	5
Intra-aortic balloon pump	10
Reoperation <2 weeks (cardiothoracic)	4
Readmission <30 days (cardiac)	12
Mortality <30 days	3
Mortality <1 yr	11
Cardiac event (patients with 1 or more)	32
Postoperative hospital stay 10 days or more	19

ICU = intensive care unit.

tients (n = 84) underwent coronary artery bypass grafting, and seven patients underwent additional valvular surgery.

Intraoperative and postoperative data, cardiac events, and the clinical end points are displayed in Table 2. The mean number of bypass grafts was 2.3 ± 1.3 . Dopamine and/or epinephrine was infused in almost half of the study group. Lidocaine infusion was necessary for seven patients. The average postoperative hospital stay was 8.7 ± 11.0 days. Thirty-two patients had some cardiac events, most of which were new postoperative arrhythmias including atrial fibrillation. Eight patients had significant postoperative ST-segment changes on electrocardiogram, and only one experienced a new Q-wave myocardial infarction. Postoperatively, 11 patients required intensive care unit stays longer than five days. Nineteen patients remained in the hospital for 10 days or more. Thirteen patients were ventilator-dependent for more than 48 h after surgery, and five had to be reintubated for respiratory distress. Ten patients required the use of an IABP. Twelve were readmitted within a month for cardiac complications, and four required reoperation within two weeks. Eleven patients died within 1 year of surgery, and three within 30 days.

Table 3 shows the correlation of preoperative BNP levels with features surrounding the perioperative phase. Preoperative ejection fraction, as determined by transthoracic echocardiogram, showed significant positive correlation with preoperative BNP levels ($p < 0.05$, $R = 0.25$) (Table 3).

Table 3. Correlations With Preoperative BNP Levels

Preoperative BNP Correlations	Pearsons R	p Value
Preoperative echocardiography ejection fraction	0.25	<0.05
Postoperative days in hospital	0.20	<0.05
Age	0.07	NS
Number of vessels grafted	0.02	NS
Preoperative number of vessels diseased	0.001	NS
Preoperative catheterization ejection fraction	−0.16	NS
Bypass time	0.14	NS
Cross-clamp time	0.07	NS

BNP = B-type natriuretic peptide; NS = not significant.

Ejection fraction calculated during cardiac catheterization ventriculography did not significantly correlate with preoperative BNP. Postoperative days spent in the hospital were also significantly correlated with preoperative BNP levels ($p < 0.05$, $R = 0.20$). There was no significant correlation between preoperative BNP levels and age, number of coronary vessels diseased or grafted, time on the cardiopulmonary bypass machine, or cross-clamp time.

As can be seen in Figure 1, the Student *t* test demonstrated a significantly higher mean preoperative BNP level in patients requiring the use of an IABP (mean BNP = 387 ± 112 pg/ml vs. 181 ± 25 pg/ml with no IABP), in patients who died within one year (357 ± 93 pg/ml vs. 184 ± 26 pg/ml in those alive), and in patients with postoperative hospital stays of 10 days or more (307 ± 68 pg/ml vs. 179 ± 27 pg/ml with stay <10 days). There were no other significant differences in mean BNP between patient groups with and without particular end points.

Figure 2 shows the three ROC curves relating preoperative BNP levels to use of an IABP, postoperative hospital stay of 10 days or more, and one-year mortality. Figure 2A displays a ROC curve for patients who required use of an

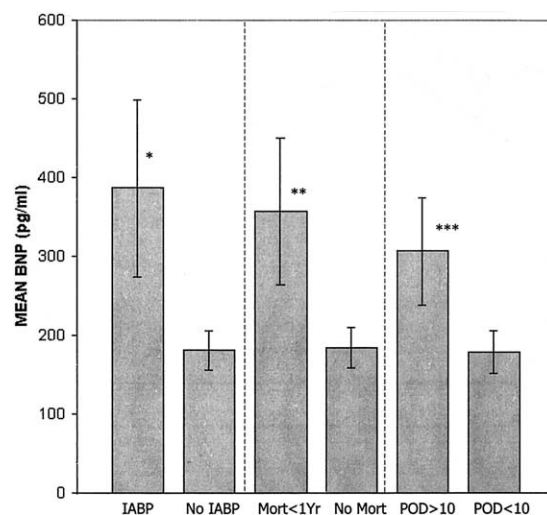


Figure 1. Preoperative B-type natriuretic peptide (BNP) levels in patients with and without particular end points (use of an intra-aortic balloon pump [IABP], mortality [Mort] within one year, and postoperative hospital duration of stay [POD] of 10 days or more). * $p = 0.015$; ** $p = 0.034$; *** $p = 0.049$.

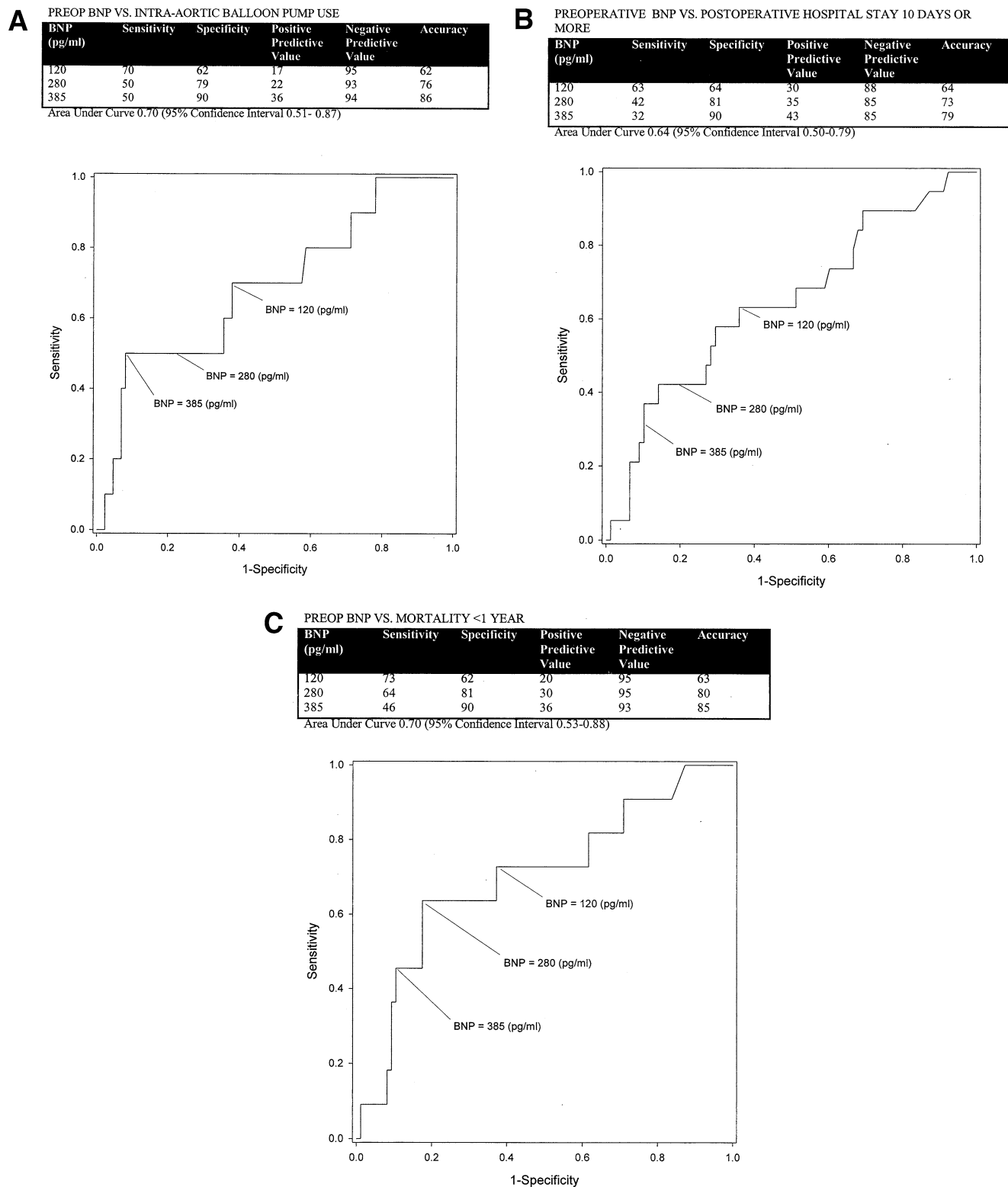


Figure 2. Receiver operating characteristic curves: preoperative B-type natriuretic peptide (BNP) levels to use of an (A) intra-aortic balloon pump, (B) postoperative hospital stay of 10 days or more, and (C) one-year mortality.

IABP. Three computer-generated BNP cut-points were examined, and sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated. The area under the curve (AUC) for this group was

0.70. A preoperative BNP of 385 pg/ml had a sensitivity of 50%, a specificity of 90%, and an accuracy of 86% for predicting the postoperative use of a pump. The lower BNP cut-points of 120 pg/ml and 280 pg/ml were more sensitive,

BNP (pg/ml)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
531	84	49	29	93	56
777	74	70	38	92	71
1055	53	88	53	88	81

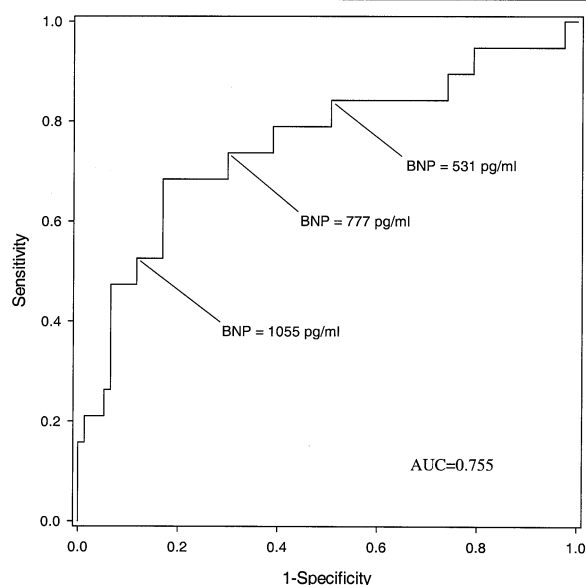


Figure 3. Receiver operating characteristic: change to maximum B-type natriuretic peptide (BNP) in patients with prolonged hospitalization (≥ 10 days) or death within one year. AUC = area under the curve.

but less specific and accurate. The ROC curve for BNP as a predictor of postoperative hospital stay of 10 days or more had an AUC of 0.64 (Fig. 2B). A preoperative cut-point of BNP of 385 pg/ml had a sensitivity of 32%, a specificity of 90%, and an accuracy of 79% for predicting postoperative stay. Figure 2C displays the ROC curve for patients who died within one year. The AUC for this group was 0.70. A BNP cut-point of 385 pg/ml had a sensitivity of 46%, a specificity of 90%, and an accuracy of 85% for predicting mortality within one year of open-heart surgery. As the data table displays, the lower cut-off BNP values were more sensitive, but considerably less specific and less accurate. The area under the ROC curve for the patients with an intensive care unit stay greater than five days was 0.64 (curve not shown). However, the significance of this curve was not within acceptable range.

Receiver operating characteristic curves were also examined to compare preoperative ejection fraction, as determined by echocardiogram, to the same clinical end points used for our preoperative BNP samples. None of these ROC curves demonstrated acceptable significance.

Receiver operating characteristic curve analysis was also used to determine the relationship between the maximum postoperative change in BNP and postoperative events (Fig. 3). Nineteen patients were hospitalized for at least 10 days, and 11 patients in this study died within one year. The sensitivity of the maximum change in BNP to predict these outcomes was 84% at the level of 531 pg/ml. The negative predictive value of the same peak change BNP level was 93%. By use of a cut-off

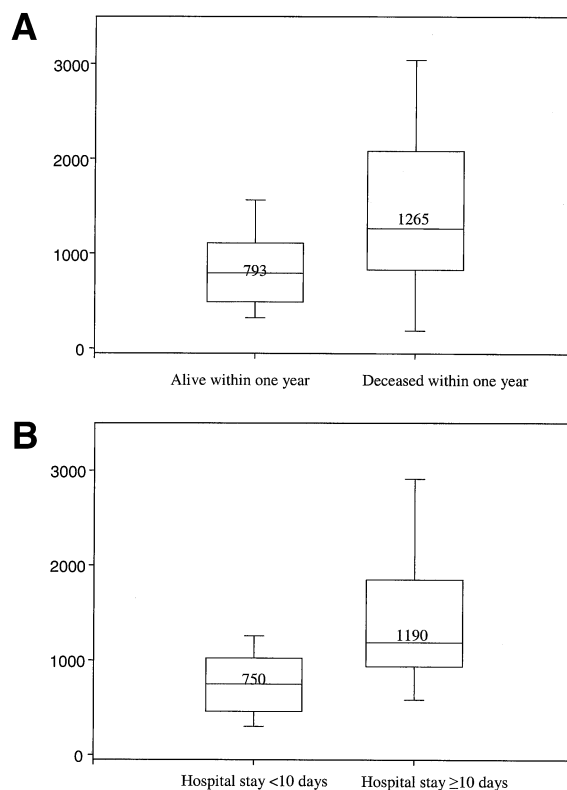


Figure 4. (A) Highest postoperative B-type natriuretic peptide (BNP) levels in patients that were alive and group that were deceased within one year. $p = 0.007$. (B) Highest postoperative BNP levels in patients that were hospitalized up to 10 days, and patients that had prolonged hospital stay (≥ 10 days) after open-heart surgery. $p = 0.0001$. The ends of the whiskers show the position of the minimum and maximum of the data, whereas the edges and line in center of the box show the upper and lower quartiles and the median. The whiskers show at a glance the behavior of the extreme outliers, whereas the box edges and midline summarize the sample in a resistant manner. Strong asymmetry in the box midline and edges suggests that the distribution is skewed and can be quantified using the Yule-Kendall skewness statistic.

value of 1,055 pg/ml, the specificity of BNP for prolonged hospital stay or death within a year was 88%.

Figure 4 shows the highest postoperative BNP level in relation to prolonged hospital stay and one-year mortality. There was a significant difference in the highest postoperative BNP levels between the group that was hospitalized < 10 days postoperatively and the group that had prolonged hospital stay for 10 or more days (750 pg/ml vs. 1,190 pg/ml, $p < 0.001$). Those two groups also showed highly significant difference in median change to maximum BNP levels (524 pg/ml vs. 960 pg/ml, $p < 0.001$).

There was also a significant difference in median levels of the highest postoperative BNP levels in 11 patients deceased within a year (1,265 pg/ml) and in patients that had undergone open-heart surgery but were alive after one year (793 pg/ml) ($p < 0.01$).

DISCUSSION

A number of risk indexes have been developed in an attempt to predict postoperative hospital stay, morbidity, and mor-

tality in patients undergoing heart surgery. Although these indexes have been extensively studied, they have been found to have questionable predictive value, accuracy, and overall usability in the clinical setting. Currently, there is no gold standard for preoperative risk assessment in heart surgery patients (5-9). Before this study, preoperative BNP has not been evaluated for its ability to predict complications in the postoperative period after heart surgery, nor has BNP ever been part of the standard preoperative work-up. Furthermore, none of the risk assessment indexes incorporate preoperative BNP levels into their calculations despite its proven correlation with ventricular dysfunction and ability to accurately diagnose HF.

Our study demonstrates that preoperative BNP levels may provide a novel advance in eliciting risk of open-heart surgery in male veterans, mainly as a way of predicting postoperative length of stay, morbidity, and mortality; BNP may be the most accurate above the level of 385 pg/ml in the preoperative evaluation for heart surgery. Although this level of BNP is higher than the cut-point of 100 pg/ml delineated in the Breathing Not Properly study for making the diagnosis of congestive HF (20), it is consistent with prognostic levels found in other studies. Harrison et al. (13) found that BNP levels above 480 pg/ml could predict future congestive HF events in patients presenting with dyspnea to the emergency department (480 pg/ml). Chang et al. (21) found a 96% negative predictive value for readmission among hospitalized patients discharged with a BNP level <420 pg/ml. Bettencourt et al. (22) found that a discharge BNP of >500 pg/ml strongly predicted rehospitalization. Further prospective studies are needed for validation of the pre-op BNP breakpoint of 385 pg/ml.

It should be noted that preoperative BNP, despite high specificity and accuracy, had low sensitivity and positive predictive value in our study. This suggests that BNP levels are best used not as a "stand-alone" test, but in conjunction with existing multivariable risk indexes.

The areas under the ROC curve for preoperative BNP as a predictor of mortality within one year (0.70) and need for IABP (0.70) are competitive with the AUC for morbidity and mortality demonstrated in Weightman's study of the modified Parsonnet's score (0.70 and 0.70), Higgins score (0.68 and 0.70), Tremblay score (0.68 and 0.67), and Tu score (0.68 and 0.69). Several studies have compared these indexes and others, with most area under ROC curve analyses within the range of 0.70 to 0.80 (5-9). As in our study, IABP use and length of hospital stay are some of the common end points used to evaluate morbidity with these indexes. It seems promising that a simple preoperative BNP level produces ROC curves that are comparable to these complex indexes. On the other hand, the risk indexes usually look at mortality within 30 days, and only our one-year mortality curve was significant. Our area under the ROC curve for mortality within 30 days was 0.69, but having only three positive subjects in our small study is the most likely explanation for this curve's unacceptable signif-

icance. Studies with more statistical power may be indicated to evaluate BNP's utility for predicting mortality within 30 days.

It is interesting that preoperative ejection fractions, although showing significant correlation with BNP, did not yield any significant ROC curves when compared with the clinical end points. It is possible that the measured ejection fractions did not correlate as much as expected with the preoperative BNP levels because the ejection fractions were determined by different methods in our study group (61 subjects by echocardiogram vs. 37 subjects by ventriculography) and, in many cases, several weeks in advance of the preoperative BNP measurement. With stronger correlation (higher R values), we would predict that the ROC curves for ejection fraction and BNP might be similar. On the other hand, it is possible that this observation is real, and, in our study group, BNP was more sensitive, specific, and accurate in predicting the clinical end points.

Study limitations. A limitation of this study was the all-male, veteran population. Further studies on larger and more diverse populations are warranted to compare predictive ability of preoperative BNP to current multivariable risk indexes and to evaluate potential for integration of this tool into preoperative evaluation. Also, two different methods were used to obtain the preoperative ejection fraction measurements. Although expensive and tedious, it would be optimal to obtain the preoperative ejection fraction using one standard test. This preoperative ejection fraction should, ideally, be measured at the same time as the preoperative BNP level—this precise coordination was not always feasible in our study.

Conclusions. In the future, physicians may be able to use these quantitative cut-off values in their decision to delay heart surgery in order to further "tune up" the patient. This might be through diuresis, in which case the BNP level could be quickly, inexpensively, and quantitatively followed until it reaches more reassuring levels. Even if this tune-up delays surgery, the physician may be preventing postoperative morbidity (i.e., balloon pumps, prolonged stay) and premature mortality. In the outpatient setting, BNP-guided therapy has been shown to be beneficial (23). Alternatively, if the patients euvoletic BNP is high, the higher patient risk might be weighed into the decision on whether or not to proceed with open-heart surgery.

A previous study has shown that a serum marker, troponin I, is useful in detecting postoperative complications (24). Similarly, we demonstrated that postoperative elevated change to peak BNP levels predicted prolonged hospital stay and death. One might speculate that the combination of a necrosis marker (troponin I) and a volume and pressure marker (BNP) might be useful for further risk stratification of patients before and in the early postoperative state.

Reprint requests and correspondence: Dr. Alan S. Maisel, VAMC Cardiology 111-A, 3350 La Jolla Village Drive, San Diego, California 92161. E-mail: amaisel@ucsd.edu.

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