Predictive value of NT-proBNP on Postoperative Outcome of Isolated Coronary Artery Bypass Patients

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Abstract

Background: High NTproBNP levels are associated with poor prognosis in heart failure and acute coronary syndromes

Aim of the study: We investigated whether pre-operative NTproBNP levels are correlated with post-operative complications in patients undergoing elective off-pump coronary artery bypass grafting.

Patients and methods: 65 consecutive patients undergoing elective off-pump coronary artery bypass grafting were recruited from 3 centers. Patients with valvular heart disease, morbid obesity, COPD, thyroid dysfunction and renal impairment were excluded. Pre-operative levels of NTproBNP were measured in venous blood samples collected before induction of anaesthesia. Patients were observed for post-operative complications till discharge form hospital

Results: The average age was 57.62 ±7.21. 86.15% of the patients were males. EuroscoreII averaged 0.76±0.34. *preoperative NTproBNP levels were* median(IQR) 160(80-397.5). levels in patients with complications were higher but didn't reach statistical significance.

Conclusion: pre-operative levels of NTproBNP were not correlated with post-operative complications in patients undergoing elective OPCAB, likely due to low complication rates in our study.

Key Words: NT-proBNP , Cardiac surgery, off-pump CABG, Complications.

Introduction

BNP is produced in both atria and ventricles, and is upregulated in failing ventricular myocardium in response to increased myocardial stretch and wall stress, together with the inactive byproduct N-terminal-proBNP (NTproBNP)[1].

Changes in hemodynamic parameters and plasma NPs levels are closely related in patients with cardiovascular diseases.The NPs system activation is modulated also by the activity of the counteregulatory neurohormonal system. Consequently, even very small changes in hemodynamics may produce significant variations in plasma concentrations of NPs[2].

The physiologic actions natriuretic peptides reduce cardiac preload and afterload to counteract the detrimental effects of pressure and volume overload seen in HF. These physiologic processes are counter-regulatory to the detrimental neurohormonal activation of the sympathetic nervous system and RAAS in HF and are why ANP and BNP levels reflect HF severity[3].

BNP concentrations were found to be independent risk markers for morbidity and mortality in patients with heart failure. In some studies NPs levels were stronger predictors of mortality and/or major cardiovascular events than left ventricular EF, NYHA class[4].

Several clinical trials have measured BNP or NTproBNP in patients presenting with acute coronary syndrome and consistently found that elevated NP values revealed important prognostic information[5].

In patients undergoing cardiac surgery, accurate risk adjustment is of paramount importance for clinical audit, benchmarking and research and to identify high-risk patients that may benefit from prophylactic interventions to reduce post-operative adverse outcomes. Although many existing clinical prognostic models such as EuroSCORE are very useful, further refinement, update or recalibration are needed to maintain their utility. Most of these clinical prognostic scores for cardiac surgery are only useful in predicting mortality but not adverse events such as AF or cardiogenic shock requiring IABP. The strength of associations between pre- operative natriuretic peptide levels and adverse outcomes after cardiac surgery varied between different studies[6].

Patients and Methods

65 consecutive adult patients registered for elective off-pump coronary artery bypass grafting OPCAB were recruited from 3 cardiothoracic surgery centers. Patients were excluded if they had signicant valvular heart disease, dilated or hypertophic cardiomyopathy, NYHA III or IV, EF < 40%, needed inotropic support or intra-aortic balloon pump before surgery, preoperative atrial fibrillation, creatinine clearance < 60 ml/min/1.73 m2, hyperthyoidism and hypothyroidism (serum TSH levels above or below reference ranges respectively. It was measured only upon clinical suspicion.), moderate to severe COPD (Shortness of breath at own pace on level, FEV1 < 80% of predicted, or continuous use of bronchodilators for > 2 weeks).

Beta-blocking agents and statins were given to all patients until the morning of surgery. Oral antiplatelets were stopped 5-7 days before surgery. Euroscore II was calculated. Venous samples for measuring NT-proBNP were collected on the day of surgery before induction. Samples were sent for analysis in Cairo University Clinical Pathology department. No specific attempts were made to standardize the anesthetic or surgical management.

After conclusion of the surgery, all patients were transferred to the intensive care unit ICU intubated and mechanically ventilated. The patients were assessed for extubation 4-8 hours after arrival in the ICU. All patients received intravenous nitroglycerin infusions for the first 24hr unless they were hypotensive. Inotropic agents were used when the patient's mean arterial pressure was below 60 mmHg and adequate perfusion could not be achieved. Potassium deficiency was promptly treated as necessary to maintain it level within 4-5mEq/L. Beta-blocking agents and statins were re-administered as soon as possible postoperatively. All samples were blindly analysed. Lab staff were blinded to the clinical conditions and dlinicians were blinded to the preoperative NTproBNP sample results.

EDTA samples were collected and plasma samples were stored in deep freezer till measured once. We used ELISA immunoassay technique that allows in vitro quantitative determination of human NTproBNP concentrations in serum, plasma and biological fluids. ELISA SET (Tecan) machine was used for reading. A curve is plotted with serial standard dilutions log graph, plotting the mean absorbance for each standard on the X-axis against the concentration on the Y-axis and draw a best fit curve through the points on the graph. (Table1 & Fig.1). Finally, the concentration of NTproBNP in the samples is then determined by comparing the OD (optical density) of the samples to the standard curve.

Table 1:

Conc. ng/mL	20	10	5	2.5	1.25	0.625	0.312	0
OD absorb.	2.622	2.36	1.63	1.048	0.658	0.4	0.258	0.06

The clinical endpoints of the study were low output heart failure (inotropic support at second post-operative day, adrenaline > 50ng/kg/min or dobutamine > 10mcg/kg/minat any time and/or need for intra-aortic balloon pump) , arrhythmias, perioperative myocardial Infarction, length of ICU, length of postoperative hospital stay, prolonged intubation (Intubation more than 24 hours postoperatively and/or reintubation following planned extubation), and mortality.

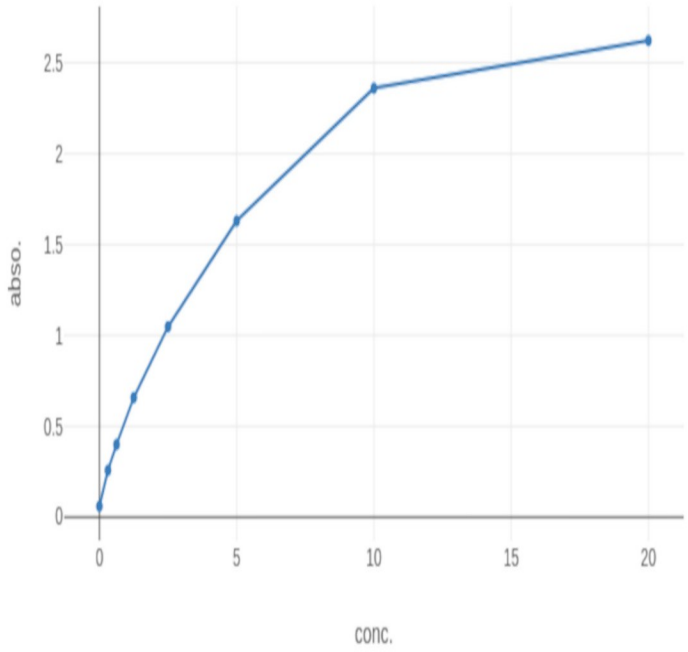

Figure 1: concentration and absorbance values of NTproBNP

An Excel spreadsheet was established for the entry of data. We used validation checks on numerical variables and option-based data entry method for categorical variables to reduce potential errors. Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Data was summarized using mean, standard deviation, median, minimum, maximum and interquartile ranage in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. Correlations between quantitative variables were done using Spearman correlation coefficient. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of NTproBNP for detection of outcomes. P-values less than 0.05 were considered as statistically significant.

Results

Sixty-five patients were recruited in this study. The average age was 57.62 ±7.21. Most of the patients were males 56 (86.15%). 10 (15.38%) had diabetes mellitus, 42 (64.62%) were hypertensive and only one had peripheral vascular disease in the form of 70% stenosis of right carotid artery. (Table.2)

Preoperative ejection fraction of patients averaged 50.91±8.13. The calculated EuroscoreII averaged 0.76±0.34. Its median was 0.68 with an interquartile range of (0.55-0.82). *The preoperative NTproBNP levels averaged* 312.41± 329.93pg/mL. The median was 160 with interquartile range of [80-397.5].

Table 2: pre-operative characteristics of patients

Variables	*Patients (N =65)*
Age in years	
- *Mean ±SD*	57.62 ±7.21
- *Median (Range)*	57 *(44 -73)*
Gender, No (%)	
- *Male*	*56 (*86.15%)
- *Female*	*9 (*13.85%*)*
Comorbidities, No (%)	
- *DM*	10 *(*15.38%)
- *HTN*	42 *(*64.62%)
- *Peripheral vascualr disease*	1 *(*1.54%)
Ejection Fraction	
- *mean ±SD*	*50.91±8.13*
- *median [range]*	*49[40-67]*
EuroScore II	
- *mean±SD*	*0.76±0.34*
- *median (IQR)*	*0.68(0.55-0.82)*

Only two patients died; one of sepsis and the other of respiratory failure. Three required prolonged mechanical ventilation, one of whom was due to delayed recovery from anaesthesia (the only patient suffering from such complication). Three suffered recent onset arrhythmia (3 Atrial fibrillation, One Ventricular Tachycardia) during their ICU stay.

One patient was re-admitted to the ICU for atrial fibrillation. Five patients had low output heart failure, and four had perioperative myocardial infarction. The mean ICU stay was 3.37±0.84 days and mean hospital stay was 6.38±1.3 days.

There were no significant differences in pre-operative NTproBNP levels in patients who had or didn't have any of the observed post-operative complications. (Table.4) Pre-operative NTproBNP didn't correlate with duration of ICU stay or post-operative hospital stay. (p>0.05)

Table 3: Rate in post-operative complications

	Count(%)
low CO	*5(7.7)*
arrhythmia	*4(6.2)*
perioperative MI	*4(6.2)*
prolonged vent	*3(4.6)*
Delayed Recovery	*1(1.5)*
mortality	*2(3.1)*

Discussion

Studies investigating the value of perioperative BNP[7][8][9][10][11] and NTproBNP[10][12][13][14][15][16][17][18][19][20][21][22] in predicting the prognosis and outocome of cardiac surgery are very heterogenous in design: the peptide used, the time and frequency of sampling, the clinical end-points, the duration of follow-up .. etc., and results.

In our study, we investigated the value of pre-operative natriuretic peptides in predicting clinical outcomes following off-pump coronary artery bypass grafting. We've chosen NTproBNP over BNP because it is accepted to be more biochemically stable than BNP. It can be drawn into glass or plastic tubes and does not require an addition of protease inhibitors such as EDTA. NTproBNP can be drawn into serum, heparin plasma, or EDTA. The intra-individual, day-to-day biologic variation in stable HF patients is about 38% for BNP and 28% for NTproBNP; in patients without HF[23].

We decided to exclude from the study population patients with factors that may influence NTproBNP levels and the post-operative morbidity. Thus extremes of age, morbid obesity, severe chronic obstructive pulmonary disease, renal impairment, ejection fraction < 40%, pre-operative artrial fibrillation and NYHA III/IV were among the exclusion criteria.

Steady-state levels of NT-proBNP are as much as four-to six-fold higher than BNP[18]. Cuthbertson et al.[16] assumed that a conversion factor of four to one between NT-proBNP and BNP is appropriate in the NTproBNP range < 400pg/mL (according to local data in their lab, n=735, Pearson's correlation coefficient=0.82, P,0.001). Chen et al.[10] used in their study both BNP and NTproBNP with pre-operative levels 103.8±184pgmL and 621.3±1050.7pg/mL, suggesting a factor of conversion aournd six. While this might not result in accurate estimates under all conditions and in all levels, it is helpful to keep that in mind while comparing different studies using different peptides.

Our study showed no significant differences in NTproBNP between patients with and without post-operative myocardial infarction. This is similar to reports by Eliasdottir et al.[15] , Schachner et al.[17] and Akhmedova et al.[22]. Attaran et al.[7] also showed similar results but, they used BNP in their study. Post-operative myocardial infarction is likely caused by intra-operative variables and are thus not captured by pre-operative natriuretic peptide levels.

Both our study and Schachner et al.[24] showed no significant differences in NTproBNP between patients with and without neurological complications. To our knowledge these are the only studies that looked into such relation. Despite cerebrovascular events and coronary artery disease sharing common etiology, other factors, such as aortic calcification and intraoperative hemodynamics heavily influence the incidence of post-operative cerebral infarctions, and these can't be reflected in pre-operative natriuretic peptide levels.

Table 4: relation between NTproBNP and post-operative complications

Complication	pre-operative NTproBNP (pg/mL) mean+-SD		
	0	0	0
Low output heart failure	*296.84+-329.75*	*490+-307.97*	*0.168.*
Arrhythmia	*306.37+-333.77*	*400+-292.91*	*0.462.*
perioperative MI	*303.79+-331.23*	*437.5+-326.22*	*0.397.*
Prolonged ventilation	*300.33+-330.69*	*550+-244.33*	*0.121.*
Delayed neurological recovery	*300.65+-319.29*	*1030*	*0.129.*
Mortality	*306.33+-331.15*	*495+-318.19*	*0.306*

Our study showed no siginificant correlation between pre-operative NTproBNP and ICU stay. This is in accordance with Chen et al.[10] , who found no significant pre-operative BNP and NTproBNP in patients with ICU stay >4 days, in a population very similar to ours; and Öztekin et al.[19], who found no signicant differences in ICU stay duration among patients with low (<100pg/mL), moderately elevated (between 100 and 500 pg/mL) and high (> 500pg/mL) NTproBNP levels. Akhmedova et al.[22] also found no significant differences in ICU stay between patients with pre-operative NTproBNP more and less than 430 pg/L.

Fellahi et al.[8] found that '[pre-operative BNP levels] *descrimination to predict a prolonged length of stay in the ICU was of ... limited value'* since their reciever operator characteristics curve ROC analysis for ICU stay > 4 days had an area under curve AUC of 0.6 denoting poor diagnostic performance. Cuthbertson et al. [16] also found weak predictive performance of NTproBNP for prolonged ICU stay > a day (odds ratio OR 1.03 as per 250pg/mL increase in NTproBNP). Indeed, they [16] found such weak numbers with almost all of the clinical end points they were investigating despite being a very large study (N=1010). Thus they concluded that '*NTproBNP levels predict early outcome after cardiac surgery*' and that '*it appears to be independent of other widely utilized methods of risk stratifications' but, 'the predictive utility is modest'* and '*its clinical validity is moderate due to its modest sensitivity and specificity it demonstrates for the outcome'*. Jogia et al.[13] reported modest, yet statisically significant correlation (r=0.59, p=0.001 and area under ROC cuve of 0.66) between pre-operative NTproBNP and length of stay in ICU. They described them as 'not strong enough to be clinically useful predictors'.

Jogia[13] reported ICU stay as 27±18hr, and Cuthbertson[16] defined prolonged ICU stay as > a day. By contrast, the centers in which we performed our study would routinely admit patients in the ICU for at least 2 post-operative days. This might have allowed their data to reflect more precisely the time needed for the patient in the ICU.

However, our study should be compared to these[8][13][16]studies with caution since they have included in their study patients with EF< 35%, NYHA III/IV and valve surgery patients.

The fact that inclusion of valve surgery can dramatically alter the diagnostic performance of pre-opreative natriuretic peptide is most clearly shown by Fellahi et al.[9] In their study[9] , which included CABG and AVR patients; ROC curve analysis of pre-operative BNP revealed AUC of 0.67 (p= 0.002) for predicting MACEs. However, when they re-analysed the data after dividing the patients into two groups, CABG

group and AVR group; preoperative BNP levels were significantly different between the groups despite other demographic data being comparable, and preoperative values of BNP were more accurate in predicting MACEs after AVR (area under ROC 0.78, p<0.001), whereas no *significant* discrimination was found for BNP values in predicting long-term adverse cardiac outcome after *CABG surgery* (area under ROC 0.54, p=0.32). Attaran[7] also found significant differences in pre-operative BNP levels in patients undergoing AVR/MVR vs CABG. And Cuthbertson[16] in multivariable analysis of pre-operative variables affecting mortality reported valve/aortic surgery±CABG having OR 3.38, and valve/aortic surgery was an independent factor predicting hospital stay > 1week with OR 1.67.

Schachner et al., 2010[24] reported statistically significant difference in ICU stay in patients who had NTproBNP levels >502pg/mL as 'In general, those patients exhibited a higher rate of comorbidities, resulting in an increased risk score'. They didn't provide any multivariable analysis to determine whether NTproBNP is and independent factor for prolonged ICU stay. And while they[24] only included in their study patients undergoing isolated CABG; older patients, and those with renal impairment and urgent surgeries where included, resulting in NTproBNP levels much higher than in our study.

Our study showed no significant differences in NTproBNP between patients with and without post-operative atrial fibrillation AF. This is similar to reports by Jogia[13], and Attaran[7].

Cuthbertson[16] reported an odds ratio of 1.02(1-1.03) per 250pg/mL increase in pre-operative NTproBNP and the development of post-operative AF (p=0.02). Apart from the fact that the value itself is of very poor diagnostic performance, the 95% confidence interval CI included 1, undermining its statistical significance.

Other studies[8][9][12] reported AF as part of a composite endpoint in the form of 'cardiac complications' or 'major adverse cardiac events' so these can't be fairly compared.

Noteworthy is the incidence of AF in our study. While the incidence of post-cardiac surgey AF is reported to be as high as 35%[25], only 4 (6.2%) of our patients developed post-operative AF. This is likely due to the lower risk factors found in our patient (patients with pre-operative AF, valvular disease and severe COPD were excluded from our study). Our patients were relatively young with good EF (mean age 57.62, EF 50.9). All had their beta-blockers on the morning of surgery and resumed them on the second post-operative day. In fact, Chen[10] reported even lower incidence of 'new onset arrhythmia' 3/76 patients (3.9%), in a population similar to ours.

Our study showed no significant differences in NTproBNP levels in patients who required or not prolonged mechanical ventilation >24hr. Öztekin[19] and Akhmedova[22] found no significant difference in ventilation time in patients with high vs low NTproBNP levels. Similarly Sindhvananda[21] found no significant differences in pre-operative NTproBNP in patients who had simple, difficult, or prolonged weaning.

This is in contrast to Liu[18] and Jogia[13] who reported 'good' correlation between ventilation time and NTproBNP levels. Yet the coefficients they calculated are rather modest, (r=0.177, p=0.009) and (r=0.46, p=0.015) respectively. Cuthbertson[16] also reported weak performance of NTproBNP in predicting the need for mechanical ventilation >24hr postoperative (OR=1.03).

Thus, earlier studies showed significant, but weak correlation between pre-operative natriuretic peptides and ventilation time, while more recent studies seem to lack that finding. One can speculate that since the correlation was weak to begin with, even minor improvements in mechanical ventilation technologies and protocols might have rendered it invalid.

Our study showed no significant correlation between NtproBNP mortality.. This is similar to Jogia[13] , and is likely due to the very low mortality count in our study (2/65 patients) and Jogia's[13] (2/118). Also most of the other studies were looking into correlations with 1month mortality [15][24][16][18][11] or long-term[24][20]

mortality, whereas we were looking into in-hospital mortality.

Schachner[24] found that NT-proBNP >502pg/mL predicted overall mortality with sensitivity 66.7% and specificity 63.9%, but they didn't report the area under curve. Recently, two large studies[20][11] looked into the predictive performance of pre-operative natriuretic peptides on mortality, in comparison with EuroSCORE II. Brynildsen[20] found that pre-operative NTproBNP >1170 pg/mL predicted with sensitivity 66%, specificity 73% and area under ROC curve 0.73, while EuroSCORE II had an area under ROC curve 0.74. Suc[11] found poor performance of pre-operative BNP in predicting mortality with area under ROC curve 0.66 compared to EuroSCORE II which had area under ROC curve 0.82. In univariate analysis, BNP was associated with mortality with an unadjusted OR of 1.06. In a multivariable analysis, however, BNP was not associated with mortality anymore. The differences between the performance of natriuretic peptides in the two studies might be explained by the duration of follow-up. While Suc[11] were looking into in-hospital mortality, Brynildsen[20] were looking into long-term mortality (961 days of follow-up). This also explains the better performance of EuroSCORE II in Suc[11] since it is actually designed and calibrated for in-hospital mortality.

Our study showed no significant differences in NTproBNP levels in patients who did or didn't developed post-operative low output heart failure. This was defined as inotropic support at second post-operative day, adrenaline >50ng.kg^{-1}.min^{-1} or dobutamine > 10µg.kg^{-1}.min^{-1} at any time and/or need for intra-aortic balloon pump. This is because many of our surgical and anaesthesia teams would use "low dose" inotropic support routinely for at least 12 hours post-operatively. Since no patient in our study needed IABP, this can be considered synonymous with need for inotropic support.

Similarly, Öztekin[19] found no differences in inotropic support among patients with low, moderately elevated and high pre-operative levels of NTproBNP in throughout a post-operative 3-day period.

Jogia[13] reported modest correlation between pre-operative NTproBNP and total perioperative noradrenaline dose (r=0.55, p=0.003) that was 'not useful as a predictor with the error of calssification almost 50%'.

This is in contrast to Eliasdottir[15] who reported that NTproBNP levels predicted inotropic support with an arrea under ROC curve was 0.84, sensitivity 79% and specificity 75% at cutoff 376pg/mL and [Akhmedova et al., 2020] [22] found significant difference in inotropic requirement between patients with NTproBNP more than and less than 430pg/mL (r=0.62). Attaran[7] also found significant differences in BNP levels in patients requiring inotropes and/or IABP.

While Krzych[26] report no significant correlation between NTproBNP and low cardiac output syndrome, they didn't define it and the numbers challenge a classical textbook definition of it. They report that 9% of their patients had low cardiac output syndrome, 7% needed IABP, while 61% needed inotropic support. However, for the need of inotropes area under ROC curve was 0.73(p<0.001), sensitivity 55.7%, specificity 82.1% at cutoff 684pg/mL.

Similar to our study, Öztekin[19] found no significant difference between patinets with low and high levels of NTproBNP in ICU or hospital stay, duration of intubation and need for inotropes. Hamed et al.[27] measured in their study pre and post-operative NTproBNP levels. They found positive correlation between post-operative NTproBNP levles and many of the post-operative clinical outcomes, however, they didn't mention any correlation between pre-operative levels and outcome.

Chen's study[10] is the most similar to ours in cohort and outcome. They reported higher, but non-significant levels of pre-operative NTproBNP in patients with prolonged ICU stay, prolonged hospitalization and major complications. 'Because elective CABG surgery was a prerequisite for enrollment … our preoperative BNP and NT-proBNP concentrations were lower than those in previous studies. This may explain why preoperative BNP and NT- proBNP are not significantly associated with outcomes.'[10]

Conclusion

Our study didn't show significant correlation between pre-operative NTproBNP and post-operative heart failure, arrhythmias, perioperative myocardial infarction, length of ICU stay, prolonged intubation, hospital stay or mortality. This is likely due to the low incidence of complications and low NTproBNP levels secondary to the predicted favorable outcomes in our patients given that they had very low risk factor.

However, through reviewing other studies we've come to the conclusion that pre-operative NTproBNP can't predict post-operative neurological complications[17] and peri-operative myocardial infarction[15][17][7][22]. This is likely because they are more dependent on intra-operative variable that can't be captured by pre-operative natriuretic peptide levels.

Pre-operative natriuretic peptides has moderate to weak[16][18] correlation with different post-operative variables. Their diagnostic performance on predicting MACEs[8][9][12] and/or mid to long-term mortality is better and more consistent across studies than with individual outcome variables. Diagnostic accuracy indices suggest that natriuretic peptides are better used as exclusion tests (low positive predictve value vs good negative predictive value).

Predictive performance is better in valvular surgery than in CABG[9] this is likely because post-operative outcome is more affected by intra-operative variables (eg. ischemia and myocardial protection) in coronary surgery.

Whether[16] or not[11] pre-operative natriuretic peptides are independent predictors of poor outcome has also been inconclusive. While this is a valid and interesting research question, it might be of less clinical relevance. Altough many existing clinical prognostic models such as EuroSCORE are very useful, most of these clinical prognostic scores for cardiac surgery are primarily useful in predicting mortality. The predictive value of natriuretic peptides on length of ICU stay and post-operative inotropic support was more consistent in centers adopting 'fast-track' protocols. An established scoring system for the prediction of morbidity and lengths of stay following cardiac surgeyr will be invaluable in resource allocation. A relatively cheap, simple, reproducible test, like natriuretic peptide measurement, we imagine; will be part of such a scoring system.

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