N-terminal pro-B type natriuretic peptide as a predictor for myocardial preservation in cases of isolated severe Aortic stenosis

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Background
Myocardial hypertrophy is a common pathologic finding in the natural history of severe aortic stenosis. A hypertrophied myocardium predisposes the patient to decreased tolerance to ischemia and increased reperfusion injury, myocardial protection is of utmost importance in patients undergoing aortic valve replacement (AVR) for severe aortic valve stenosis.
Myocardial protection techniques during cardiac arrest have been extensively investigated in the clinical setting of coronary revascularization. However, fewer studies have been carried out on patients affected by left ventricular (LV) hypertrophy, where the choice of type, and temperature of cardioplegia remains controversial.
Aim
The study investigates preoperative N-terminal pro-B type natriuretic peptide (NT pro-BNP), its relation to Troponin I levels, and whether it can predict a preferred cardioplegic solution by comparing the short-term outcomes of the two commonly used blood and Histidine-Tryptophan-Ketoglutarate (HTK) cardioplegic solutions in patients undergoing aortic valve replacement for severe aortic stenosis.
Patients and methods
A total of 72 patients will be randomly allocated into two groups; group (A=36) received HTK solution, and group (B=36) received blood cardioplegia. All anesthesia protocols are unified among all patients. All surgical procedures were conducted on a cardioplegic arrested heart via standard median sternotomy, utilizing full Cardiopulmonary bypass (CPB) via aorto-atrial cannulation and LV venting through a left atrial catheter under moderate hypothermia (28–32°C) by topical cooling.
Results
There was no statistically significant difference found between group A and group B regarding post-operative ejection fraction (EF) and newly developed postoperative Regional wall motion abnormalities (RWMA).
There was no statistically significant difference found between group A and group B regarding the percentage of patients with atrial fibrillation, ventilation hours, and exploration while there was a statistically significant increase in troponin, I level in group B than group A.
There was a statistically significant negative correlation between NT pro-BNP preoperative and aortic valve area (AVA) and also with ejection fraction preoperative while there was a statistically significant positive correlation found between NT pro-BNP and troponin I preoperative and postoperative.
Conclusion
HTK solution and Blood cardioplegia both offer sufficient protection for the myocardium. NT pro-BNP serves as a sensitive indicator for predicting the results and effectiveness of different cardioplegia types

Keywords:
aortic valve surgery, histidine-tryptophan-ketoglutarate, and N-terminal pro-B-type natriuretic peptide

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Introduction

Severe symptomatic aortic stenosis (AS) has a bleak prognosis and no medical treatment exists. As the population ages, the clinical importance and burden of AS are increasing, yet its diagnosis and management

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are multifaceted, especially in the era of percutaneous interventions. AS is characterized by progressive valve narrowing, which clinically manifests as dyspnea, syncope, and angina despite normal coronary arteries. However, symptomatology is subjective and confounded by comorbidities (particularly in the aging population) [1].

The presence of AS induces an abnormal and protracted pressure overload upon the left ventricle, that results in systolic and diastolic dysfunction. These abnormalities exacerbate the well-known adverse myocardial remodeling occurring with age. In the early phase of AS the main compensatory mechanisms are represented by concentric left ventricular hypertrophy (LV) and elevation of end-diastolic pressure. The protracted pressure overload induces changes in the myocardial extracellular matrix leading to progressive myocardial fibrosis and decreasing LV compliance. Thus, the initial adaptive remodeling becomes maladaptive with increased LV hypertrophy, myocardial fibrosis, heart failure, and worsening prognosis [2].

B-type natriuretic peptide (BNP) and the prohormone N-terminal pro-B-type natriuretic peptide (NT pro-BNP) are released from the myocardium in response to ventricular or atrial stretch. Studies evaluating BNP and NT pro-BNP in AS have demonstrated an association with echocardiographic findings of severe AS (peak velocity, mean gradient, aortic valve area) symptoms, the risk for symptom onset, risk for death, need for aortic valve replacement (AVR), cardiovascular hospitalization, and abnormal exercise hemodynamics. Markers of Cardiac Injury Troponin elevation reflects the release of cardiac-specific contractile filaments in the setting of myocardial –necrosis or cell membrane injury. Hemodynamic obstruction from aortic stenosis can lead to increased myocardial oxygen demand leading to oxidative stress, cardiac injury, and troponin release [3]

The study investigates preoperative NT pro-BNP, its relation to Troponin I levels, and whether it can predict a preferred cardioplegic solution by comparing the short-term outcomes of the two commonly used blood and Histidine-Tryptophan-Ketoglutarate (HTK) cardioplegic solutions in patients undergoing AVR for severe aortic stenosis.

Patients and methods

The study conducted in the cardiothoracic surgery department, at Ain Shams University Hospital. A total of 72 patients randomly allocated into two groups; group (A=36) received HTK solution, and group (B=36) received blood cardioplegia. All patients underwent preoperative echocardiographic examinations, had their preoperative NT pro-BNP serum levels measured, and also had Troponin I levels assessed.

All patients received the same routine preoperative investigations as perinstitutional protocol.

Anesthesia and operative technique

All anesthesia protocols unified among all patients. All surgical procedures conducted on a cardioplegic arrested heart via standard median sternotomy, utilizing full Cardiopulmonary bypass (CPB) via aorto-atrial cannulation and LV venting through a left atrial catheter under moderate hypothermia (28–32°C) by topical cooling.

The study's inclusion criteria encompassed patients undergoing elective, isolated, primary AVR for severe aortic stenosis (AS). The definition of severe high gradient AS included a peak velocity of greater than or equal to 4 m/sec, a mean pressure gradient (MPG) of greater than or equal to 40 mmHg, and an aortic valve area (AVA) of less than or equal to 1 cm^2, as determined through two dimensional echocardiography. On the other hand, several exclusion criteria were applied, such as patients declining to participate with informed consent, individuals below the age of 18 or above 55 years, those with morbid obesity (body mass index > 35), and individuals with a low ejection fraction (EF) ($\leq$45%). These criteria were designed to ensure a specific and relevant patient population for the study's investigation into myocardial protection during AVR in the context of severe aortic stenosis and LV hypertrophy.

Myocardial protection

One of the following 2 cardioplegic solutions will be used for myocardial protection.

HTK solution

Solution: Custodiol (Custodiol; Koehler Chemi, Alsbach-Haenlien, Germany).

Dose: Custodiol HTK will be delivered at 3–4°C, 20 ml/kg to a maximum of 2 liters for the initial dose; subsequent doses are delivered at 3–4°C, 10 ml/kg to a maximum of 1 liter after 120 min

Components: 15 mmol/l sodium chloride, 9 mmol/l potassium chloride, 4 mmol/l magnesium chloride,

18 mmol/l histidine hydrochloride, 180 mmol/l histidine, 2 mmol/l tryptophan, 30 mmol/l mannitol, 0.015 mmol/l calcium chloride, 1 mmol/l potassium hydrogen 2-ketoglutarate, osmolarity 310 mOsm/kg, pH 7.02–7.20.

Blood cardioplegia

Solution: prepared by clinical pharmacy division according to institutional protocol.

Dose: Blood cardioplegia will be delivered at 3–4°C, 10–15 ml/kg for the initial dose; subsequent 5 ml/kg doses are delivered at 3–4°C every 40 min

Components: mixed at a ratio of 4 : 1 (Blood/ Cardioplegic solution), contains the following: 200 ml ringer acetate, 30 meq/l potassium chloride, 100 mg xylocaine, and 25 meq/l sodium bicarbonate.

Measurement of cardiac marker Troponin I

Collection: venous blood sampling.

Timing: Blood samples will be collected before induction of anesthesia and 24 h postoperatively.

Measurement of cardiac marker NT pro-BNP

Collection: venous blood sample

Timing: Blood sample will be collected before induction of anestheisa.

The serum levels of Troponin I and NT pro-BNP are determined utilizing PATHFAST cTnI-II (cardiac Troponin I) and PATHFAST NT pro-BNP test (LSI medicine corporation, Tokyo, Japan).

Both tests are based on CLEIA (Chemi-luminescence Enzyme Immuno-Assay). Using the device Compact immunoanalyzer(Mitsubishi chemical medicine, Tokyo, Japan)

Statistical analysis

The data was entered into the Statistical Package for Social Science. The quantitative data were presented as mean, standard deviations, and ranges when parametric and median, and inter-quartile range (IQR) when data was found non-parametric. Rephrase Qualitative variables were presented with percentages and numbers. The comparison between groups with qualitative data was done by using the χ^2 test and Fisher exact test instead of the χ^2 only when the expected count in any cell was found less than 5. The comparison between two groups with quantitative data and parametric distribution was done by using an Independent *t*-test while the comparison between two groups with quantitative data and non-parametric distribution was done by using the Mann-Whitney test. The One Way ANOVA test was used to compare the two groups. The correlation between two quantitative parameters was assessed using Spearman correlation coefficients. The confidence interval was set to 95% and the margin of error accepted was set to 5%.

Results

This prospective parallel group randomized clinical study was conducted on 72 patients admitted to the cardiothoracic surgery department, at Ain Shams University Hospitals in the period from November 2020 to December 2022.

The propensity matched patients (criteria: age, sex and BMI) were no different in terms of comorbidities (DM, HTN, smoking), symptoms (NYHA classification and syncopal attacks), and preoperative labs (Troponin and NT pro-BNP levels).

Echocardiographic finding were no different except for group B showed higher mean pressure gradient across the stenotic AV (Table 1).

All of them underwent the AVR procedure with antegrade infusion of cardioplegic solution. Most of the intraoperative parameters were statistically different. There was a significantly longer cross clamp time and higher number of ventricular fibrillation incidents in the HTK solution group (A). However group B showed more need to use inotropic support post clamp removal Table 2.

In the postoperative period there was no statistical difference in analyzed parameters. However troponin levels were significantly higher in the blood cardioplegia group B Table 3.

Discussion

Although single-administration cardioplegic solutions are particularly needed in complex or minimally invasive surgeries, they can also be effectively observed in simpler procedures such as AVR for severe aortic stenosis. This procedure offers an ideal setting due to patients having similar clinical profiles. Despite the relatively short cross-clamp time during the surgery, achieving cardioprotection may be challenging because of the presence of hypertrophied myocardium and alterations in endomyocardial

Table 1 Comparison between group A and group B regarding preoperative variables

Parameter	Group A (*n*=36)	Group B (*n*=36)	*P*-Value
Age (y)	44.6±8.4	45.1±8.3	0.791
Male (n, %)	15 (41.7%)	19 (52.8%)	0.345
BMI	28.61±0.96	29.06±1.66	0.168
Syncope (n, %)	8 (22.2%)	11 (30.6%)	0.422
NYHA Classification			0.267
- I (n, %)	6 (16.7%)	4 (11%)	
- II (n, %)	15 (41.7%)	10 (27.8%)	
- III (n, %)	9 (25%)	17 (47.2%)	
- IV (n, %)	6 (16%)	5 (13.9%)	
Diabetes Mellitus (n)	9	16	0.083
Hypertension (n)	11	8	0.422
Smoker (n)	13	7	0.114
Creatinine (mg/dl)	0.88±0.05	0.90±0.05	0.179
Troponin I (cTnI) (ng/ml)	0.23 (0.09–0.42)	0.32 (0.09–0.43)	0.639
NT pro-BNP (pg/ml)	924.75±314.83	967.81±420.61	0.624
Aortic Valve Area (cm^2)	0.65±0.02	0.66±0.02	0.300
Ejection Fraction (EF) (%)	58.22±3.41	59.75±3.68	0.072
Left Ventricular Mass Index (g/m^2)	145.5±4.19	144.63±6.44	0.60
Mean Pressure Gradient (mm Hg)	65.14±4.16	62.61±4.42	0.015

Table 2 Comparison between group A and group B regarding intraoperative parameters

Parameter	Group A (*n*=36)	Group B (*n*=36)	*P*-Value
Aortic Cross Clamp Time (min)	56.5±1.82	54.11±4.01	0.0097
Spontaneous Rhythm Restoration Post Clamp Removal (*n*, %)	18 (50.0%)	28 (77.8%)	0.014
Temporary Pacemaker (*n*, %)	10 (27.8%)	11 (30.6%)	0.795
Use of Inotropic Support During Surgery (*n*, %)	27 (75.0%)	14 (38.9%)	0.002

Table 3 Comparison between group A and group B regarding postoperative parameters

Parameter	Group A (*n*=36)	Group B (*n*=36)	*P*-Value
EF (Mean±SD)	54.78±4.05	55.92±4.98	0.291
New post-RSWA			1.00
– Global hypokinesia	1 (2.8%)	1 (2.8%)	
Mortality	1 (2.8%)	2 (5.6%)	0.555
ICU Stay (Median (IQR))	2 (2–4.5)	2.5 (2–3.5)	0.805
Ventilation Hours (Median (IQR))	12 (10–24)	12 (11–24)	0.945
Troponin I (Median (IQR))	3.1 (2.9–3.2)	3.2 (3.2–3.3)	0.026

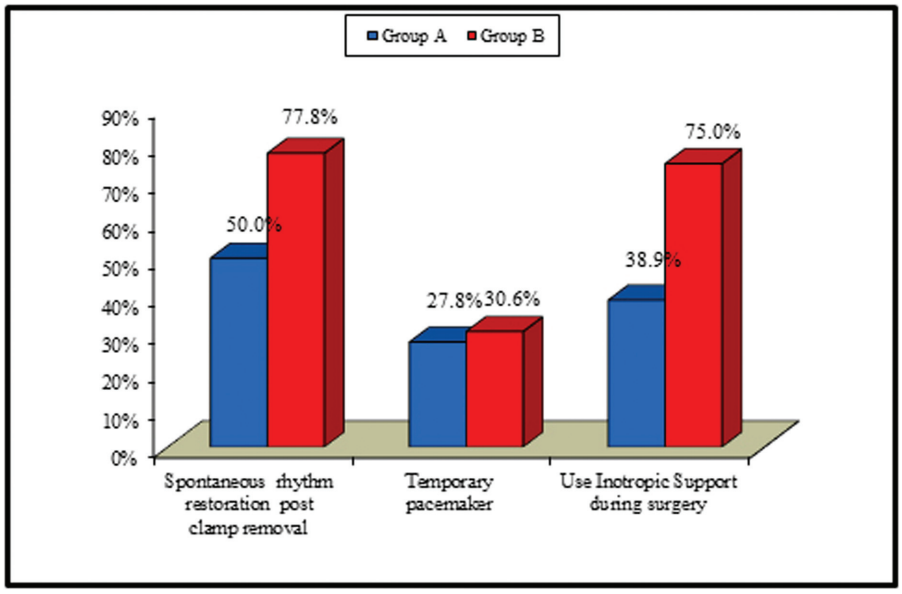
perfusion. These factors can impact the efficacy of cardioprotection measures in this context.

Taking the intraoperative variables into analysis (Fig. 1) the aortic cross-clamp time was longer in group A than in group (B)., Hoyer *et al.* [4] published their findings, which stated that the median cross-clamp duration for HTK was 55 min and that for blood cardioplegia, it was 52 min.

The findings indicate that group (A) had a reduced occurrence of spontaneous rhythm restoration after the clamp removal. In a recent systematic study by Edelman *et al.* [5], they reported a tendency towards a significant increase in ventricular fibrillation (VF) incidence. Furthermore, six out of the eight trials demonstrated a higher VF occurrence in the Bretschneider group following cross-clamp removal. Usage of inotropic support during surgery is significantly higher in group B. In comparison, there was no discernible variation in the use of inotropes between the groups in the research conducted by Lee *et al.* [6].

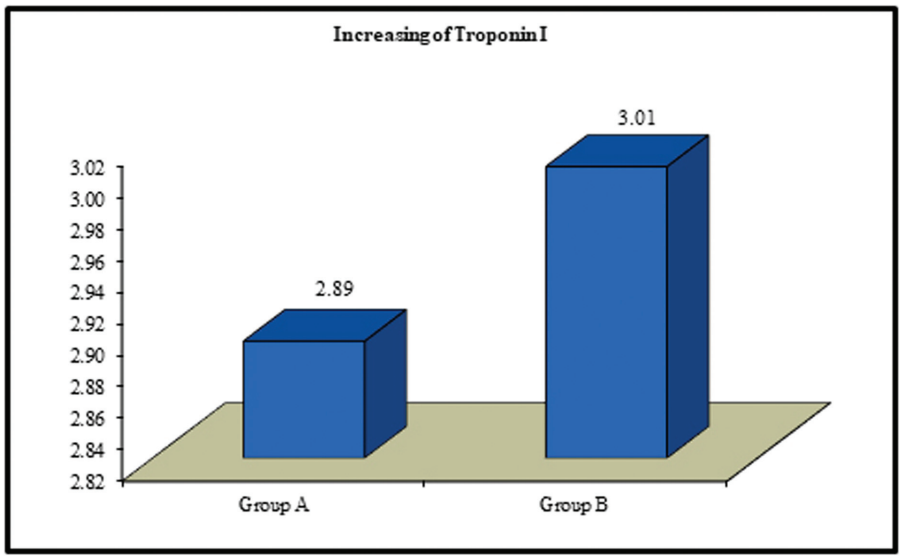
The indicators of myocardial preservation through cardioplegic solutions are essential for evaluating the

Figure 1



Comparison between group A and group B regarding spontaneous rhythm restoration postclamp removal, temporary pacemaker and use of inotropic support during surgery.

Figure 2



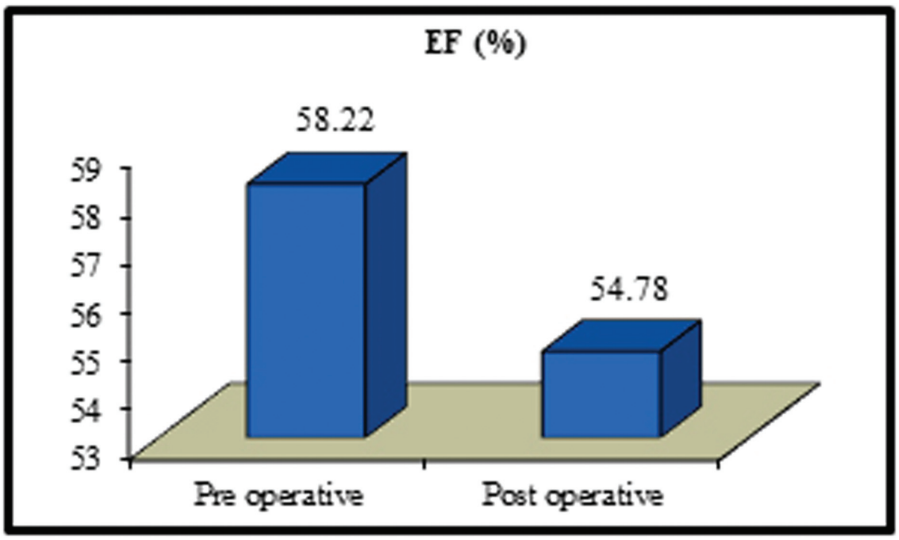
Comparison between group A and group B regarding mean difference of troponin I.

effectiveness of these solutions during cardiac procedures. These indicators include monitoring cardiac biomarkers, assessing LV function, analyzing histological changes, observing ECG patterns, measuring myocardial oxygen consumption, evaluating myocardial enzymes and inflammatory markers, and measuring cardiac output.

During the investigation of Troponin I (cTnI) in the study, no significant changes were observed between the groups during the preoperative period. However, in the postoperative phase, there was a notable and statistically significant increase in group B (Fig. 2).

Alternatively, Braathen and Tonnessen [7] conducted a prospective randomized trial to determine the most effective type of cardioplegia for providing myocardial protection in isolated AVR for aortic stenosis (AS). The study revealed that using 'crystalloid cardioplegia' instead of 'blood cardioplegia' led to significantly higher blood levels of cardiac marker proteins like CK-MB and troponin. These findings were

Figure 3



Comparison between the level of Ejection Fraction(%) pre and postoperative in group A.

consistent with the research conducted by Chee-Hoon Lee *et al.* [8], who compared the effects of HTK solution and blood cardioplegia in 314 patients undergoing AVR for isolated aortic stenosis.

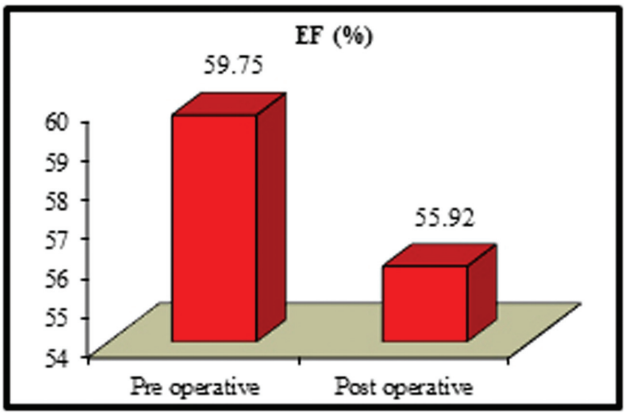
Additionally, Crestanello JA *et al.* [9] reported their findings comparing the Bretschneider HTK solution with a traditional cardioplegia approach, and Krzysztof Sanetra *et al.* [10] conducted a recent study to assess the efficacy of del Nido cardioplegia. In patients receiving AVR for isolated aortic stenosis, the mean differences in CK-MB and TnI did not show significant variations across groups compared to the HTK treatment.

As for the postoperative EF, there were no significant variations between the groups. However, both groups experienced a statistically significant decrease in EF from the preoperative period to the postoperative period (Figs 3 and 4). Despite this drop, there was no statistically substantial difference between the two groups regarding the extent of the EF change.

Concerning newly manifested regional wall motion abnormalities (RWMA), each group included one patient (2.8% of the total patients) with global hypokinesia. There was no statistically significant difference between the two groups in terms of the development of RWMA.

Moreover, there were no significant differences between the two groups in the early postoperative outcomes, including the incidence of atrial fibrillation, the number of ventilation hours, the duration of stay in the intensive care unit, or premature death.

Figure 4



Comparison between the level of Ejection Fraction(%) pre and postoperative in group B.

Plasma BNP as a predictor of postoperative outcome

In cardiac surgery both preoperative and postoperative levels of NT pro-BNP and BNP have been associated with adverse outcomes, treatment with inotropes and mechanical circulatory support [11–13].

Severe LV hypertrophy (LVMI $> 180\,g/m^2$), EF less than or equal to 50%, and age more than 75 years and small aortic annulus area were predictors of complications in the early postoperative periods.

BNP moderately linked to LV function: positive correlation with LV end-diastolic and end-systolic

diameters, negative correlation with LV fractional shortening and LVEF

Strong BNP-LVMI correlation in aortic stenosis. Elevated afterload triggers LV myocyte hypertrophy, impacting postoperative function and mortality. BNP may serve as a prognosticator after AVR [14].

Our research findings confirms the relation between NT pro-BNP and the established predictors, there is a statistically significant inverse link between NT pro-BNP and the area of the aortic valve, as well as a correlation with EF; however, there is no statistically significant relationship with the mean pressure gradient. Plasma levels of NT-propeptides were shown to have an inverse connection with AVA before AVR in the research by Qi *et al.* [15].

Also, there was a statistically significant rise in the preoperative level of NT pro-BNP in patients who received inotropic support during surgery. In contrast, the level was lower in those patients whose spontaneous rhythm was restored after the clamp was removed. At the same time, no statistically significant difference was discovered between the usage of a temporary pacemaker and the length of time the aortic cross-clamp time.

A link may be considered statistically substantial between NT pro-BNP and the preoperative and postoperative troponin levels. The findings of this study demonstrate a significant inverse relationship between NT pro-BNP and postoperative EF.

No link was found to be statistically significant with the other evaluated factors, such as ventilation hours, postoperative atrial fibrillation, time spent in the intensive care unit, total time spent in the hospital, or in-hospital mortality.

The efficacy of BNP in predicting early outcomes following valve replacement was investigated by Bergler-Klein *et al.* [16] using 79 symptomatic patients who were having surgery simultaneously. They discovered that an increased neurohormone plasma level was linked to a considerably more significant proportion of deaths from any reason; six out of 79 patients died while undergoing surgery. These patients had a median BNP value substantially more effective than the survivors. These findings have been recently substantiated by Eliasdottir *et al.* [17] Table 4.

NT pro-BNP as a predictor for myocardial preservation

While it may be challenging to directly detect significant differences in cardiac injury among hearts arrested with cardioplegia, the release of biomarkers remains a key and valuable indirect method for assessing myocardial damage

In our study, we investigated indicators of myocardial preservation to make a comparison between two distinct cardioplegic solutions. Throughout the surgical procedure and in the postoperative period, we closely monitored the utilization of inotropic support more than 24 h and the decline in EF. These observations served as essential parameters in assessing the efficacy of the cardioplegic solutions in preserving the myocardium during the surgical intervention.

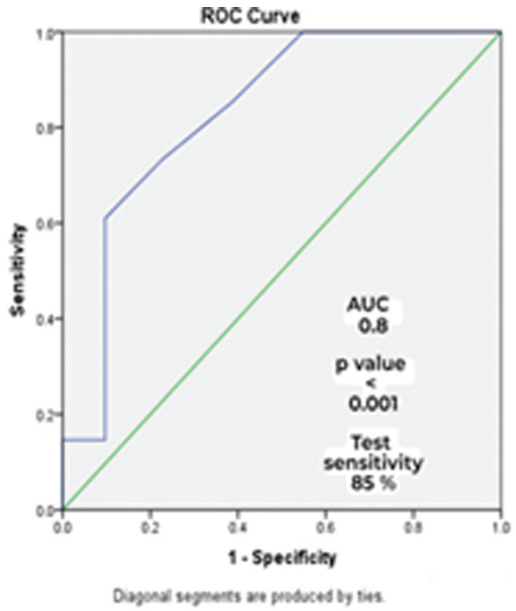
Regarding the use of inotropic support, 41 out of the 72 patients required inotropic support during the study. The group B patients showed a significant increase in the need for inotropic support compared to other groups. To predict the necessity for inotropic support, we employed preoperative levels of NT pro-BNP (Fig. 5) and troponin (Fig. 6) and used the receiver operating characteristic (ROC) curve analysis. Both NT pro-BNP and troponin proved to

Table 4 Correlation of N-terminal pro-B-type natriuretic peptide level preoperative with the other studied parameters preoperative, postoperative

Preoperative Troponin I (cTnI) (ng/ml)	NT pro BNP (pg/ml) before surgery *r*	 *P*-value
EF (%) PRE	-0.311*,*	0.008
Left ventricular mass index (gm/m2)	0.4120	0.00032
Aortic valve area (cm^2)	-0.283*	0.016
Post		
Troponin I 24 h postoperative	0.627**	<0.001
EF POST	-0.265*	0.025
Postoperative outcome		
ICU stay	0.010	0.931
Ventilation hours	0.033	0.784

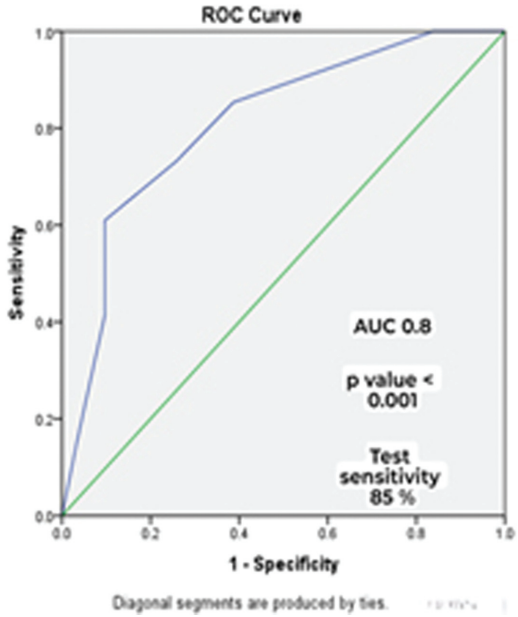
* significant. ** highly significant.

Figure 5



Receiver operating characteristic curve for N-terminal pro-B-type natriuretic peptide level as predictor for use of inotropes.

Figure 6



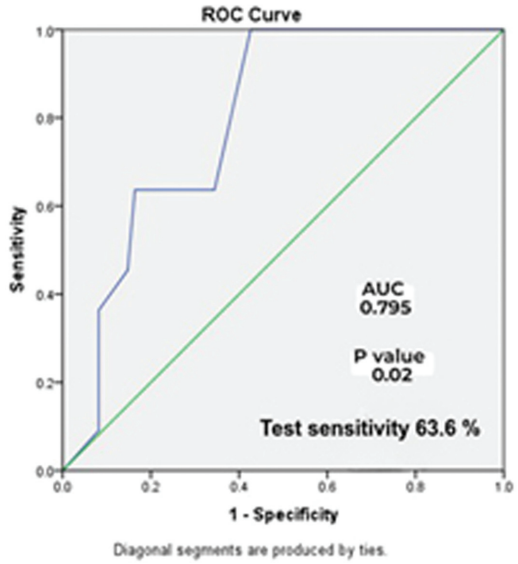
Receiver operating characteristic curve for Troponin I level as predictor for use of inotropes.

be significant predictors, with a *P*-value less than 0.001 and the same test sensitivity of 85%. This indicates that both biomarkers are valuable in identifying patients who might require inotropic support postoperatively, providing crucial insights for clinical management.

In our study, we established cutoff values for troponin and NT pro-BNP levels to determine the need for increased inotropic support. A troponin level of 0.1 ng/ml and an NT pro-BNP level of 817 pg/ml were identified as the critical thresholds. Patients with troponin levels above 0.1 ng/ml and NT pro-BNP levels exceeding 817 pg/ml required more frequent utilization of inotropic support during the postoperative period. These cutoff values serve as essential guidelines in identifying patients at higher risk of needing additional cardiac support and can aid clinicians in making timely and appropriate treatment decisions.

In our investigation of postoperative EF, we found that only 11 patients exhibited impaired EF (EF less than 50%), and there was no significant difference between the two groups. To predict EF impairment, we utilized the ROC curve analysis with preoperative levels of both NT pro-BNP (Fig. 7) and troponin (Fig. 8). Interestingly, NT pro-BNP demonstrated a more significant predictive capability for EF impairment with a *P* value of 0.02, whereas troponin showed a less significant value of 0.6. Despite this difference, both biomarkers had the same sensitivity in the tests,

Figure 7

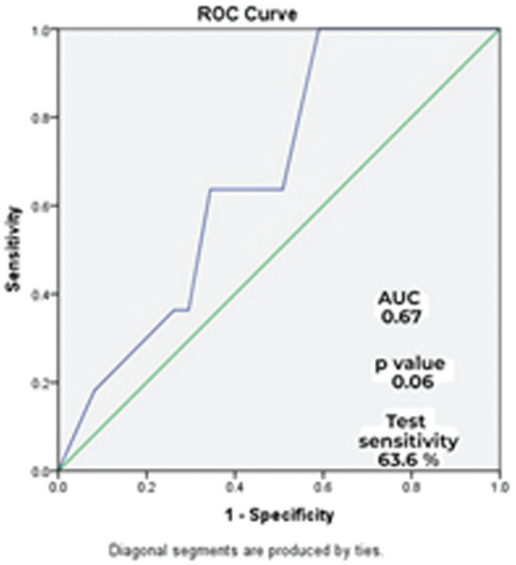


Receiver operating characteristic curve for N-terminal pro-B-type natriuretic peptide level as predictor for impaired Ejection Fraction%.

reaching 63.6%. These findings suggest that NT pro-BNP may serve as a more effective predictor of postoperative EF impairment compared to troponin.

The findings from our study indicate that NT pro-BNP, using a cutoff level of 876 pg/ml, appears to be a more reliable predictor of postoperative EF impairment compared to troponin, which uses a cutoff level of 0.22 ng/ml

Figure 8



Receiver operating characteristic curve for Troponin I level as predictor for impaired Ejection Fraction%.

As mentioned earlier, based on the suggested cutoff value of NT pro-BNP (817 pg/ml), we recommend the use of HTK solution as it demonstrated a reduced need for inotropic support compared to the other solution. Additionally, there was no significant difference observed between the two solutions in terms of postoperative EF. These results suggest that HTK solution may offer better myocardial preservation and potentially lead to a decreased requirement for inotropic support during the postoperative period, while still maintaining comparable postoperative EF outcomes when compared to blood cardioplegia

Conclusion

Both HTK solution and blood cardioplegia are effective in preserving the myocardium during AVR surgery. NT pro-BNP, a biomarker sensitive to cardioplegia's effectiveness, can be used as a predictor. For optimal preservation with HTK, a suggested threshold of NT pro-BNP above 817 pg/ml is encouraged.

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Conflicts of interest
There are no conflicts of interest.

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