

## Better cardioprotection in atrial septal defect patients treated with cardiopulmonary bypass beating heart technique without the application of aortic cross clamp

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### Abstract

**Background and objectives:** Creatine phosphokinase-myocardial band fraction (CPK-MB) and cardiac troponin I (cTnI) are cardiac specific biochemical markers which are raised in myocardial ischemia. The aim of this study was to determine cardiac injury by comparing the levels of cardiac enzymes CPK-MB and cTnI in atrial septal defect (ASD) patients whose operative repair was done under cardiopulmonary bypass (CPB) using beating heart technique with and without the application of aortic cross clamp.

**Materials and Methods:** This study was carried out in the Department of Cardiothoracic and Vascular Surgery in a Tertiary Care Hospital over a period of 2 years. A total of 60 atrial septal defect (ASD) patients were operated and repair of the defect was done under the CPB using beating heart technique. Aortic cross clamp was applied in 22 patients (Group-A) while 38 patients were operated without cross clamp (Group-B) during the procedure. Blood samples were collected 24 hours prior and 12 hours post procedure for the estimation of CPK MB and cTnI levels.

**Results:** Mean age of the atrial septal defect patients was 23.83±10.97 years and 60% and 40% of the patients were females and children (age < 18 years) respectively. Serum CPK-MB and cTnI levels were in the normal range in all the patients before surgery and increased significantly post procedure. Twelve hours after surgery, the mean CPK-MB and cTnI levels were significantly low in Group-B patients compared to Group-A patients (CPK-MB: 56.39±23.55 U/L vs. 34.38±15.97U/L, p= 0.0004; cTnI: 9.37±4.97 ng/ml vs. 5.92±4.17ng/ml, p = 0.009).

**Conclusion:** Post surgery CPK-MB and cTnI levels were significantly higher in ASD patients who underwent CPB surgery with aortic cross clamp compared to those in whom aortic cross clamp was not applied. Therefore, application of aortic cross clamp during the procedure induces greater levels of ischemic injury to the heart.

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### Introduction

Atrial septal defect (ASD) is the third most common congenital heart disease [1]. ASDs comprise 30 to 40% of all congenital heart diseases in adults [2]. MSX1 gene has been found strongly associated

with the development of ASD [3]. Normally, an interatrial septum separates the upper chambers of the heart namely right and left atrium. ASD occurs because of the failure of closure of communication between the right and left atria [4]. ASDs are

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classified into various types based on the location of the defect in interatrial septum [5]. Most common type is the ostium secundum ASD which is due to enlarged foramen ovale or septum secundum not completely formed. Ostium primum type of ASD is usually associated with AV canal defects. A sinus venosus ASD occurs in the inflow portion of superior and inferior vena cava. It is usually associated with anomalous pulmonary venous drainage into the right atrium [6].

Surgical repair of ASD is safe and effective with minimal morbidity and mortality [7]. It involves closure of the septal defect under CPB. In beating heart technique aortic cross clamp may or may not be applied during the procedure. Advantage of using beating heart technique is to prevent or minimize ischemic-reperfusion injury to myocardium [8]. Ischemic myocardial injury during cardiac surgery may cause cardiac stunning and dysfunction which is one of the consequences and can cause delay in the postoperative recovery.

CPK-MB and cTnI are cardiac specific markers and their levels increase during myocardial ischemia. CPK-MB levels rise within 4 to 8 hours of ischemia or acute myocardial infarction and return to normal in 48 to 72 hours. Biological reference interval is <4.88 U/L. cTnI is a cardiac-specific protein and is a highly sensitive marker of myocardial ischemic damage. Its levels rise in serum within 3 to 4 hours of myocardial ischemia and remain elevated up to 10 days. Its biological reference interval is <0.040 ng/ml. Some ischemic myocardial injury does occur even in the beating heart surgery despite continuous warm blood perfusion to the coronary arteries and is manifested in the form of rise in the levels of CPK-MB and cTnI.

The aim of the study was to determine cardiac injury by comparing the levels of cardiac biomarkers CPK-MB and cTnI in ASD patients in whom operative repair was done under CPB using beating heart technique with continuous normothermic perfusion with and without the application of aortic cross clamp.

### **Material and methods**

This prospective study was carried out in the Department of Cardiothoracic and Vascular

Surgery, Sheri Kashmir Institute of Medical Sciences (SKIMS), Srinagar- a Tertiary Care Hospital in collaboration with the Department of Immunology and Molecular Medicine, SKIMS. The study was conducted over a period of 2 years from June 2016 to May 2018 and was approved by the Institutional Ethical Committee of SKIMS. Informed verbal consent was obtained from all individual participants included in the study. In case of children ( $\leq 18$  years of age), consent was obtained from the parents/guardians.

*Study population and surgical procedure:* ASD patients of both genders were included in the study. Patients were properly evaluated. Coronary angiography was performed in patients above 40 years of age with complaints of chest pain or having risk factors for coronary artery disease. Patients with coronary artery disease, recent myocardial infarction were excluded from the study. Enrolled patients were randomly assigned to Group-A and Group-B. Surgical repair of the defect was performed in all patients under CPB using beating heart technique. Aortic cross clamp was applied to the aorta in Group-A patients. In Group-B patients, ASD repair was performed without applying aortic cross clamp.

The main aim of using the beating heart technique was to minimize ischemic-reperfusion injury to the myocardium. Approach was standard midline sternotomy. After heparinization, total CPB was instituted by cannulating ascending aorta and both venae cavae. An antegrade high flow cannula was inserted into the ascending aorta to facilitate high flow perfusion during the procedure. Continuous normothermic perfusion to coronaries was provided through aortic root cannula with a 5 ml/kg/min normothermic oxygenated blood continuously in patients of both groups. Left atrium was kept filled with the blood to prevent air embolism from occurring. Cardioplegia was not administered in any of the patients. Primary repair was done in patients with small atrial septal defects while in larger defects a patch repair was done either with pericardium or prosthetic materials. General anesthesia was similar in both groups with routine systemic arterial and central venous pressure monitoring. Same cardiopulmonary bypass machine with a roller pump and CPB circuit

with membrane oxygenator from the same manufacturer was used in all patients. Electrocardiographic changes were monitored and recorded throughout the procedure.

**Estimation of CPK-MB and cTnI:** Twenty four hours before surgery, two samples of 3ml arterial blood were collected in two separate specialized tubes and were sent for estimation of CPK-MB and cTnI levels by CLIA (chemiluminescence immunoassay) method. Similarly, 12 hours after surgery, two samples of 3ml arterial blood were collected again for estimation of CPK-MB and cTnI levels by CLIA method.

**Data Analysis:** Microsoft Excel and SPSS 20 were used for data analysis. Student's t-test and ANOVA were used for p value determination. p value ≤0.05 was considered significant.

**Results**

Beating heart ASD repair was done in 60 patients over a period of 2 years. This included 24 children (age ≤ 18 years; mean age 13±4.18 years) and comprised 40% of the total patient population. Of the total cases, 60% of patients were females. Group-A and B consisted of 22 (36.6%) and

38(63.3%) patients respectively. Ages varied from 5 to 45 years. Predominant age groups were 10-19 (33.3%) and 30-39 (26.7%) years. Mean age of the Group-A and B patients was 21.77±10.75 and 25.02±11.05 years respectively (Table-1).

Primary repair was done in 34 (56.6%) atrial septal defect cases which mainly included small defects ≤20 mm. Although this also included 15 cases with defect sizes in between 20 to 30 mm. Patch repair was done in larger defects either with pericardium or synthetic material (PTFE). Pericardial patch repair was done in 15 (25%) and PTFE patch repair in 11 (18.3%) patients. Table-2 shows levels of CPK-MB and cTnI post surgery in patients with different sizes of atrial septal defects. Levels of these biomarkers did not correlate with the sizes of the defects and were not significantly (p>0.05) different.

Table-3 shows the serum CPK-MB and cTnI level in Group-A and Group-B patients before and after ASD repair surgery. Twenty four hours prior to surgery serum CPK-MB and cTnI levels were in normal range in all (both Group-A and B) the patients. Twelve hours post surgery, both serum CPK-MB and cTnI levels were raised in all the patients of both groups. Group-A patients in whom

**Table-1:** Age distribution of study patients (n=60)

| Age groups (Years)       | Group A (n=22)<br>n (%)    | Group B (n=38)<br>n (%)    | Total (n=60)<br>n (%)      |
|--------------------------|----------------------------|----------------------------|----------------------------|
| 0 to 9                   | 3 (13.6)                   | 3 (7.9)                    | 6 (10)                     |
| 10 to 19                 | 7 (31.8)                   | 13 (34.2)                  | 20 (33.3)                  |
| 20 to 29                 | 4 (18.1)                   | 7 (18.4)                   | 11 (18.3)                  |
| 30 to 39                 | 6 (27.3)                   | 10 (26.3)                  | 16 (26.7)                  |
| 40 to 49                 | 2 (9.1)                    | 5 (13.2)                   | 7 (11.7)                   |
| Mean age ± SD<br>(Range) | 21.77 ± 10.75<br>(5 to 42) | 25.02 ± 11.05<br>(6 to 45) | 23.83 ± 10.97<br>(5 to 45) |

**Table-2:** Post surgery serum CPK-MB and cTnI levels in patients with different sizes of atrial septal defects (n=60)

| ASD size (mm) | Number | CPK MB (U/L) Mean ± SD | cTnI (ng/mL) Mean ± SD |
|---------------|--------|------------------------|------------------------|
| < 10          | 1      | 94.25                  | 21.78                  |
| 10 to 19      | 18     | 37.42 ± 19.20          | 6.02 ± 4.39            |
| 20 to 29      | 26     | 44.60 ± 22.67          | 7.28 ± 4.84            |
| 30 to 39      | 11     | 41.57 ± 17.80          | 6.97 ± 2.86            |
| 40 to 49      | 4      | 40.54 ± 23.79          | 8.74 ± 5.34            |

Note: p>0.05, as calculated by ANOVA.

**Table-3:** Serum CPK-MB and cTnI levels in ASD cases before and after the operation with and without the application of aortic cross clamp

| Group   | Number | CPK- MB (U/L)    |                 | cTnI (ng/mL)     |                 |
|---------|--------|------------------|-----------------|------------------|-----------------|
|         |        | Before Operation | After Operation | Before Operation | After Operation |
| Group-A | 22     | 0.02 ± 0.01      | 56.39 ± 23.55   | 0.008 ± 0.003    | 9.37 ± 4.97     |
| Group-B | 38     | 0.05 ± 0.03      | 34.38 ± 15.97   | 0.003 ± 0.002    | 5.92 ± 4.17     |
| p value |        | 0.12             | 0.0004          | 0.60             | 0.009           |

Note: Group-A: operated with aortic cross clamp; Group-B: operated without aortic cross clamp. p value calculated by Student's t- test.

aortic cross clamp was applied had significantly more mean serum CPK-MB and cTnI levels compared to Group-B patients who were operated without aortic cross clamp (CPK-MB: 56.39±23.55 vs. 34.38±15.97 U/L, p=0.0004; cTnI: 9.37±4.97 vs. 5.92±4.17 ng/mL, p=0.009 respectively; Table-3).

## Discussion

Beating heart surgery on CPB is safest and one of the best forms of myocardial protection. Main advantage of using the beating heart technique in ASD repair is to minimize ischemic injury to the myocardium [8]. In conventional heart surgery cardioplegic solutions used to arrest the heart lead to ischemic-reperfusion myocardial injury and cardiac stunning. Some myocardial damage does occur even in beating heart surgery despite no use of cardioplegic solutions and use of continuous warm blood perfusion. Rise in the levels of cardiac biochemical markers such as CPK-MB and cTnI in beating heart surgery does suggest some myocardial injury as a result of ischemia. The results in this study showed a rise in the levels of both CPK-MB and cTnI post surgery in the patients of ASD repair. Average levels of these cardiac markers were significantly more in the patients in whom aortic cross clamp was applied during the procedure than those patients in whom aortic cross clamp was not applied. It may be inferred from this study that myocardial protection is better in ASD patients undergoing beating heart ASD repair without aortic cross clamp. Application of aortic cross clamp appears to increase myocardial ischemic injury. Siaplaouras and colleagues [9] studied perioperative myocardial damage by

measuring cTnI levels serially before and after surgery in the pediatric population undergoing elective cardiac surgeries for congenital heart defects. The study demonstrated that it was an important determinant for postoperative cardiac function and recovery. A study by Swaanenburg et al. [10] estimated CPK-MB and cTnI levels postoperatively to determine the myocardial injury and found that the levels of cardiac biochemical markers depend upon the type of cardiac surgery and duration. There are similar studies which correlate increased postoperative CPK-MB and cTnI levels with the adverse effect and postoperative recovery [11,12,13]. CPK-MB and cTnI levels can increase many fold compared to baseline levels depending on the duration of the procedure [10,15]. Cardiac troponin I was found very useful in predicting the postoperative course in terms of length of ICU and postoperative hospital stay of the patients undergoing mitral valve surgery [16]. The levels of cardiac biomarkers namely CPK-MB and cTnI in CPB surgery significantly correlated with the type of cardiac surgery and also upon the cross clamp time [14,17]. Also, beating heart technique in ASD repair offers early extubation and discharge from the hospital [18]. Using aortic cross clamp during ASD repair done under CPB and beating heart technique seems to increase myocardial ischemic injury as is evident from the high levels of cardiac biomarker levels in this study.

There were certain limitations of this study. First, sample size was small and second it was a single centre study and might not reflect the experience in other centers. Also, the effect of duration of surgery on biochemical marker levels was not taken into consideration.

ASD patients in whom operative repair was done under CPB using beating heart technique without the application of aortic cross clamp suffer significantly less myocardial injury as was evident by the lower levels of cardiac biochemical markers namely CPK-MB and cTnI 12 hours post surgery compared to ASD repair with aortic cross clamp. However, some degree of ischemic injury to myocardium does occur in both techniques.

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