

# Impact of Variable Types of Preconditioning Upon Inotropic Score in Adult Patients Undergoing Cardiac Valve Replacement Surgery: A Randomized Clinical Trial

MAHMOUD ABD EL-AZEZ, M.D.\*; EMAD Z. KAMEL, M.D.\*; MOHAMED MAHMOUD, M.D.\*\* and SALMA I. AHMED, M.Sc.\*

*The Departments of Anesthesiology, Intensive Care & Pain Management\* and Cardiothorathic Surgery\*\*, Faculty of Medicine, Assiut University, Assiut, Egypt*

## Abstract

**Background:** The objective of this study was to validate the impact of cardiac preconditioning (ischemic versus pharmacological) upon postoperative inotropic score in adult patient undergoing open heart surgery.

**Aim of Work:** Is to validate the impact of Sevoflurane versus ischemic & Sevoflurane pc upon postoperative inotropic score in adult patient undergoing open heart surgery.

**Material and Methods:** Thirty ASA II-III adult undergoing open heart surgery were included in the study. They were randomly allocated into 2 groups, Group A (15 patients). Anaesthetized by Sevoflurane as a pharmacologic preconditioner, Group B (15 patient) ischemic preconditioning was done after induction and before cardiopulmonary bypass by inflation the cuff of blood pressure above 200mmHg in the lower limb every 5min for 3 cycles.

**Results:** Non significant difference between the two groups regarding to the inotropic score and ICU stay.

**Conclusion:** Both ischemic and pharmacological cardiac preconditioning could offer some sort of cardiac protection reflected upon inotropic score.

**Key Words:** Preconditioning – Cardiac surgery – Inotropic score.

## Introduction

ISCHEMIC heart disease is one of the major causes of morbidity and mortality all over the world. Various medical and surgical strategies have been evolved to reduce the mortality from acute myocardial infarction [1].

Preconditioning (PC) of the heart occurs when brief exposure to a stimulus protects the heart from subsequent ischemia. PC stimulus may be (ischemic, pharmacologic or Physical) [2]. Pharma-

logical PC may be induced by variable agents e.g. (Sevoflurane, isoflurane, opioidsetc). Ischemic PC includes local and remote ischemic stimulus. The idea is temporary interruption of blood supply to the organ so that liberation of protective mediators occurs. The liberated mediators have favorable effects not only upon the myocardium but, it extends to protect other organs against inflammatory activation what's called ischemia reperfusion injury [3].

Inotropic Score (IS) is already an evident predictor of postoperative cardiac morbidity and mortality after cardiac surgery [4]. We investigated the implications of both types of preconditioning upon IS as a primary goal focus.

## Material and Methods

This prospective, randomized, double blind, comparative study was conducted in Assiut University Hospital in the period between March 2016 and September 2017 after IRB approval from the Medical Ethic Committee, Faculty of Medicine, Assiut University, Assiut, Egypt in. Trial registration was prospectively undertaken in clinical trial. [gov](https://www.clinicaltrials.gov) (ID: NCT03105089). A written informed consent was obtained from the patients before their participation in the study. All collected data were confidential and were used for the purpose of scientific research only.

Thirty patients aged more than 18 and less than 60 ASA (II and III), and were scheduled for open heart (valve replacement) surgery under general anesthesia. Exclusion criteria included emergency surgery, clinically significant kidney or liver disease, prolonged CPB time (>120min), the need for

**Correspondence to:** Dr. Salma I. Ahmed,  
[E-Mail: doctorselma9@gmail.com](mailto:doctorselma9@gmail.com)

intra-aortic balloon pump, post-operative major cardiac events e.g. serious arrhythmia or bleeding that required surgical re-exploration.

Randomization done through web-based randomizer and patients were equally randomized into two groups. Group A (n=15 patients) anaesthetized by Sevoflurane as a pharmacologic preconditioner. Group B (n=15 patient) ischemic preconditioning was done after induction and before cardiopulmonary bypass by inflation the cuff of blood pressure above 200mmhg in the lower limb every 5min for 3 cycles, with maintenance of anesthesia by total intravenous anesthesia. All cardiac medication were continued up to the night before surgery with addition of 1.5mg promazepam and stoppage of any angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

*Anesthesia:* Monitoring included Oropharyngeal temperature, pulse oximetry, end-tidal Co<sub>2</sub>, 5 leads ECG, central venous pressure, invasive arterial blood pressure, and urine output. Induction was done with sleeping dose propofol 1mg/kg, 1-2mg midazolam, 1:2  $\alpha$ g/kg fentanyl, and cisatracurium intubating dose of 0.15-0.2mg/kg. Maintenance: (Sevoflurane 1:2% in air-oxygen mixture in ratio of 1:1 in Group A, and in Group B we used total intravenous anesthesia composed of propofol infusion in a dose of 70  $\alpha$ g/kg/min along with midazolam 10  $\alpha$ g/kg/min Group B), and in both groups cisatracurium 0.03mg/kg/30 minutes for maintenance of muscle relaxation and fentanyl infusion 1  $\alpha$ g/kg/hr.

Cardiopulmonary Bypass (CPB) circuit was primed with mannitol, sodium bicarbonate, and packed red cells to obtain a hematocrit 26%. Heparin 400-500IU/kg was administered and once Activated Clotting Time (ACT) reached > 450 seconds, CPB was initiated. The aorta was clamped and the cardioplegic solution was administered into the aortic root and the patient core temperature was allowed to decrease down to 30-32°C. A Mean Arterial Pressure (MAP) was maintained between 60±10mmHg during CPB. At the end of the intracardiac procedure, re-warming was started, aortic cross clamp removed, pacing or defibrillation was performed depending on heart rate and rhythm. Ventilation was resumed, hemodynamics and arterial blood gases were optimized, then the patient was weaned from CPB at 37°C. Protamine was administered to reverse heparin in a dose of 1mg protamine for every 100IU heparin. The patients were then transmitted to ICU.

The criteria for extubation were as the standards for post-operative cardiac patients in the form of adequate level of consciousness, hemodynamic stability, absence of arrhythmias, adequate airway reflexes, normothermia, acceptable mediastinal drainage blood volume, and acceptable blood gas.

Health care personnel providing post-operative care, and patients were blind to the patient's group assignment. Post-operative inotropic score was calculated according to Wernowsky IS.

IS = Dopamine dose ( $\alpha$ g/kg/min) + Dobutamine dose ( $\alpha$ g/kg/min) + 100 X epinephrine dose ( $\alpha$ g/kg/min) [5].

#### *Statistical analysis:*

The primary endpoint of this study was the postoperative Wernowsky IS scores. Based on previous studies, a target sample size was calculated. A power analysis estimated that a sample size of 15 patients in each group would have an 80% power at the 0.05 level of significance to detect a statistically significant difference between groups in the primary outcome parameter. Distribution of baseline variables was assessed by the Shapiro-Wilk tests. Continuous data were reported as mean  $\pm$  SD and were analyzed using independent sample *t*-test. Categorical data were reported as percentages and were analyzed using the Chi-square test. Non-parametric data were analyzed using the Mann-Whitney U-test. A *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS statistics Version 20 (SPSS Inc., Chicago, IL, USA).

#### *Inotropic score:*

Since the admission to the PACU till end of the study, there was no significant difference in inotropic score between study groups. However, the significant difference was found within each group; in both groups there were significant changes in inotropic scores in 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> days, (Table 2), Fig. (1).

## **Results**

There were no significant differences between groups in the demographic data regarding age, gender, BSA, echocardiographic data, bypass time, aortic crossclamping time, icu stay (Table 1).

There was no significant difference between groups in inotropic score but significant change from the basal value within the same group (Table 2) Fig. (1).

Table (1): Patients' demographic data.

Item	Group A (n=15)	Group B (n=15)
<i>1- Age "yrs.":</i>		
Mean ± SD (Min-max)	44.60±12.50 (19.0-61.0)	41.00±15.80 (22.0-70.0)
<i>2- Gender:</i>		
Male	8 (53.30%)	11 (73.3%)
Female	7 (46.70%)	4 (26.70%)
<i>3- BSA Kg/m<sup>2</sup></i>		
	1.75±0.21	1.70±0.19
<i>Echocardiography:</i>		
EF	62.67±10.22	60.20±9.21
Fractional shortening	34.01±12.30	34.01±10.11
PASP	38.13±12.33	37.00±10.01
Bypass time (min)	113.87±4	115.27±5
Aortic cross clamping	80.21±10.31	84.22±10.02
ICU stay (days) ± SE	4.1±0.38	4.3±0.35

Data are expressed as mean ± SD, percentage, or ratio. *p*-value (*p*>0.05) is consider non-significant.

Table (2): Inotropic score in study groups.

Item	Group A (n=15)	Group B (n=15)
IS. day 1	9.71±2.74	7.22±1.82
IS. day 2	6.16±1.47*	4.21±1.24***
IS. day 3	2.71±0.80**	2.15±0.67**
IS. day 4	2.33±1.31*	1.02±0.35*
IS. day 5	0.63±0.66	0.55±0.25

- Data is expressed as mean ± SE. IS inotropic score. *p*-value (*p*>0.05) is consider non-significant.

\*: Significant change from the basal value within the same group.

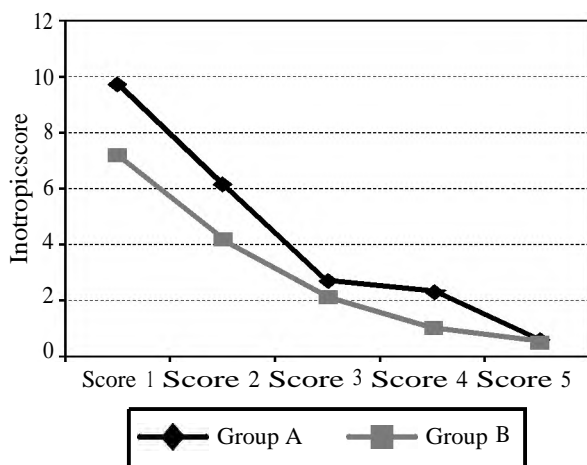


Fig. (1): Inotropic score in study groups.

### Discussion

This study covered the role of remote (ischemic and pharmacological) preconditioning (RIPC) in decreasing inotropic score and ICU stay of patient in the setting of complex cardiac bypass surgery or valve lesion.

The length of ICU and hospital stay and the inotrope score are factors which can be influenced by operative and anesthetic factors and which have an important impact on health-care resources. The inotrope score provides an objective measurement of the requirement of inotropes in immediate post-operative period. Data on inotrope requirement was collected daily from the medical drug chart on the ICU and calculated at 0 (time when coming off bypass), 24, 48 and 72h after the surgery using the formula: Wernowsky IS=Dopamine dose (  $\mu\text{g/kg/min}$ ) + Dobutamine dose (  $\mu\text{g/kg/min}$ ) + 100 X epinephrine dose (  $\mu\text{g/kg/min}$ ) [5]. In our study there was non significance difference regarding Inotropic Score between study groups however, the significant difference was found within each group; in the form of significant decreases in inotropic score in the 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> day. This agrees with [6] who reported that remote ischemic preconditioning may impact on study outcome measures by reducing hospital stay, inotropic score and length of hospital stay. (Derek, et al.) who investigate the effect of (RIC) on one year clinical outcomes in 1610 high risk patients undergoing CABG ± valve surgery recruited via 27 tertiary cardiac centers in the UK. Patient is <18 years old; scheduled for valve ± CABG surgery with blood cardioplegia and those patients randomized to receive RIC will have a standard blood pressure cuff placed on the upper arm inflated to 200mgHg for 5 minute and then deflated for 5 minute a cycle which was performed 4 times in total.

Volatile anesthetics to various degrees have been shown to decrease myocardial contractility and myocardial oxygen demand, it explain cardio protection against ischemia and reperfusion [7].

However, these anesthetics were also found to induce cardio protection via mechanisms that are similar to pathway involved in ischemic preconditioning [8].

The use of isoflurane during cardiac surgery has been complicated by a controversial issue associated with isoflurane-induced coronary steal.

This phenomenon describes collateral blood redistribute away from ischemic areas, thus suggesting that isoflurane would exacerbate the ischemic insult in an already compromised myocardial region [9].

Earlier studies about the myocardial protective of isoflurane have approved protective action to improving metabolism possibly by blocking L-type Ca<sup>2+</sup> channels [10] preserving energy-rich phosphates [11], vasodilatation of coronary vessels,

and to reduce expression of the adhesion molecules [12]. However, there were reports that isoflurane offered no protection against reperfusion injury in vivo [13].

Although there are reports that sevoflurane does not induce preconditioning-like cardio protection [14] others have reported that it does and the effect is mediated by mitochondrial KATP channel opening [15]. This type of preconditioning occurs after long-term hypothermia, and independent of cardioplegic solution used [16].

Myocardial protection by sevoflurane could also be related to its anti-inflammatory effect. For example, pretreatment of hearts with sevoflurane reduces intracoronary platelet adhesion most likely via an endothelial mechanism [17]. For more detailed reviews on mechanisms of anesthetic preconditioning [7,18-22].

In our study there was no difference between pharmacological and ischemic preconditioning in decreasing inotropic score and ICU stay on the statistical study.

#### *In Conclusion:*

Both ischemic and pharmacological cardiac preconditioning could offer some sort of cardiac protection reflected upon inotropic score and ICU stay of patient undergoing open heart surgery. Ischemic preconditioning is superior to the other techniques at limiting myocardial necrosis during CABG. Pharmacological preconditioning may offer some benefit but this was not statistically.

#### *Conflicts of interest:*

The Authors declare that there is no conflict of interest.

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## تأثير الأنواع المختلفة من التهيئة الأولية للقلب على معاميل جرعات محفزات إنقباض القلب في مرضى عمليات القلب المفتوح البالغين

التهيئة الأولية للقلب تحدث عندما يتعرض لمؤثر يحميه من الإقفار-المؤثر يمكن أن يكون (إقفار-دوائى-بدنى).

التهيئة الأولية الدوائية يمكن أن يحدث بالأنواع المختلفة للعقاقير (السيوفلورين-الإيزوفلورين-المورفين).

التهيئة الأولية بالإقفار تتضمن نوعين (موضعى-وبعيد) والفكرة في ذلك هي قطع التغذية الدموية للأعضاء وينتج عن ذلك تحرر بعض من الوسطاء الوقائيين اللذين لهم تأثير مناسب لا يقتصر على عضلة القلب فقط بل يتسع لوقاية الأعضاء الأخرى.

معاميل جرعات محفزات إنقباض القلب يتنبئ بالنسبة المرضية والموتى بعد العملية.

تم إستبعاد المرضى الذين يعانون من مرض مزمن فى الكلى أو الكبد أو حالة طارئة فى القلب أو آن وقت المريض على الإنعاش القلبية الرئوية تعدى ١٢٠ دقيقة أو من يحدث لهم مضاعفات خطيرة بعد العملية مثل عدم إنتظام ضربات القلب بطريقة خطيرة أو النزيف الشديد الذى لا يتوقف إلا بإعادة فتح القلب مرة أخرى.

تم إختبار المرضى وعددهم ٣٠ مريضاً من الذين يخضعون لجراحة القلب المفتوح وقسمت عشوائياً إلى مجموعتين، المجموعة الأولى ١٥ مريضاً تم تخديرهم بواسطة عقار السيوفلورين كمؤثر للتهيئة الأولية للقلب ونوعه دوائى والمجموعة الثانية تم إستخدام الإقفار كمؤثر للتهيئة الأولية للقلب بعد بدء التخدير وقبل وضع المريض على الإنعاش القلبية الرئوية وذلك بواسطة نفخ صفة جهاز قياس الضغط أعلى من ٢٠٠ مم زئبقى فى الطرف السفلى للمريض كل خمس دقائق لمدة ٣ دورات.

لا توجد فروق ذات دلالة إحصائية بين المجموعات فى معاميل جرعات محفزات إنقباض القلب وفترة إقامته بالعناية المركزة بين مجموعتين الدراسة.

كلا من المؤثرين (الإقفارى-الدوائى) للتهيئة الأولية للقلب يحدث تقدماً نوعاً ما فى حماية القلب وتقليل معاميل جرعات محفزات إنقباض القلب وتحسين وظائف القلب، التنفس والجهاز المناعى.