

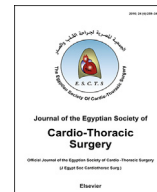
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Journal of the Egyptian Society of Cardio-Thoracic Surgery

journal homepage: <http://www.journals.elsevier.com/journal-of-the-egyptian-society-of-cardio-thoracic-surgery/>

# Role of intra-aortic morphine in post conditioning during valvular surgery with low ejection fraction

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## ARTICLE INFO

### Article history:

Received 31 July 2017

Received in revised form 4 September 2017

Accepted 16 September 2017

Available online xxx

### Keywords:

Valve

AVR

MVR

Morphine

Post conditioning

## ABSTRACT

**Background:** The application of cardioplegia does not completely eradicate myocardial ischemia in cardiac/reperfusion injury due to cardiac arrest. Post conditioning is novel strategy of attaining cardioprotection. Pharmacological post conditioning using a drug as morphine administered before reperfusion would protect the heart against ischemia-reperfusion injury. We investigated whether intra-aortic morphine administration has a post conditioning effect on patients with low ejection fraction (EF) undergoing valve surgery.

**Methods:** This prospective randomized controlled trial in a single center involved one hundred patients scheduled for elective valve surgery were divided into two groups: the Post conditioning group and the Control group. The Post conditioning group (n = 50) received a dose of morphine (0.1 mg/kg) diluted in 20 ml normal saline, injected via a cardioplegia needle into the aortic root with warm hotshot before aortic cross-clamp removal while the control group (n = 50) received the same volume of saline without morphine. Both groups received antegrade warm blood cardioplegia. To assess results EF, fractional shortening (FS), troponin level, ABG, inotropes, postoperative ventilation time, and length of ICU stay were assessed.

**Results:** Postoperative EF and FS revealed a statistically significant higher readings in the Post conditioning group. A significant reduction in the troponin levels was recorded in the study group than the control group. Duration of postoperative ventilation and length of ICU stay were statistically lesser in the Post conditioning group.

**Conclusions:** Morphine administration immediately with warm hotshot was related to improvement in the cardiopulmonary function, less inotropic drug use, and higher left ventricular EF.

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## 1. Introduction

Although the application of cardioplegia is an effective strategy for cardio-protection, yet it does not completely eradicate myocardial ischemia/reperfusion injury during cardiac arrest [1]. In spite of prolonged myocardial ischemia alone can jeopardize the structural and biochemical integrity of the cells, limited oxygen deprivation is usually associated with only

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Peer review under responsibility of The Egyptian Society of Cardio-thoracic Surgery.

<https://doi.org/10.1016/j.jescts.2017.09.001>

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Please cite this article in press as: Omran AM, Role of intra-aortic morphine in post conditioning during valvular surgery with low ejection fraction, Journal of the Egyptian Society of Cardio-Thoracic Surgery (2017), <https://doi.org/10.1016/j.jescts.2017.09.001>

transiently depressed myocardial contractility [2]. Paradoxically, the restoration of blood flow after sustained myocardial ischemia results in a phenomenon known as myocardial ischemia-reperfusion (I-R) injury, where in the tissue injury after reperfusion is greater than that produced by ischemia alone [2].

I-R is a major determinant of myocardial impairment in post cardiac surgery patients. Thus, effective prevention during reperfusion may reduce cardiac injury [3].

Prevention is by conditioning of the myocardium by stimulation of innate cardio protective mechanisms by short periods of non-lethal ischemia that prepare tissue for a longer period of ischemia. The conditioning stimulus can be applied before (preconditioning), during, or immediately after (post conditioning) the longer 'desired' ischemia [4].

Ischemic post conditioning (IPC) (*brief periods of ischemia alternating with brief periods of reflow applied at the onset of reperfusion following desired ischemia*) is a very simple as well as safe maneuver, but it is difficult to routinely apply it in practice and hence the idea of pharmacological post conditioning using medications appears through using drugs given at the time of early reperfusion [5].

One of the popular drugs used in pharmacological conditioning is morphine. Morphine administered before or with reperfusion would protect the heart against I-R injury [3].

Most of the studies targeted morphine as post conditioning in coronary artery bypass graft (CABG) patients; in this study we studied the effect of using morphine on valvular patients with low ejection fraction.

## 2. Patients and methods

A prospective randomized single center control study involving 100 patients done at National Heart Institute, Egypt between 2014 and 2016, these patients were scheduled for elective valve surgery.

Patients were randomly divided into either a post conditioning group, group A (n = 50) or a control group, group B (n = 50), in a single blinded study.

### 2.1. The inclusion criteria

The Inclusion criteria: were patients with Mitral, Aortic, Tricuspid valve lesion or their combinations with EF ( $\geq 25$  and  $\leq 40\%$ ) who were scheduled for elective primary surgery.

### 2.2. The exclusion criteria

The exclusion criteria included patients with ischemic heart disease, aortic aneurism, pulmonary hypertension, emergency surgery and patients with preoperative hemodynamic instability as well as patients with impairment of renal or hepatic function or previous stroke and patients with suspected iatrogenic coronary injury during the surgery as coronary ostia injury during aortic valve surgery.

All the operations whether single or multiple valve repair or replacement were done in the same anesthetic and surgical techniques using antegrade intermittent warm blood cardioplegia every 15–20 min delivered through a separate head from the pump.

Immediately before aortic cross clamp (ACC) removal, all patients received warm blood as warm hot shot for 3 min.

The post conditioning group (n = 50) received a dose of morphine (0.1 mg/kg) diluted in 20 ml normal saline, injected via a cardioplegia cannula into the aortic root with the warm hotshot while the control group (n = 50) received the same volume of saline without morphine.

Ejection fraction (EF) and fractional shortage (FS) were measured by transthoracic echocardiography (TTE), immediately after patient being transferred to intensive care unit (ICU), prior to ICU discharge and 6–12 months later. Also, the need for inotropic support for weaning from bypass and postoperatively in the ICU, were assessed in addition, incidence of new arrhythmia (rather than preoperative atrial fibrillation (AF) in Mitral patients), or epicardial pacing for weaning from bypass and postoperatively were assessed.

Cardiac troponin I (6–8 h) after ICU admission, mean ABG (arterial blood gases) were also measured as well as duration of postoperative mechanical ventilation in hours and length of ICU stay in days.

### 2.3. Statistical analysis

Data were analyzed using SPSS© Statistics version 22 and MedCalc© version 13.

The D'Agostino-Pearson test was used to examine the normality of numerical data distribution. Normally distributed continuous variables were presented as mean and SD, and intergroup differences were compared using the independent-samples (unpaired) t test. Discrete variables and skewed continuous variables were presented as median and interquartile range, and differences were compared using the Mann-Whitney test. Categorical variables were presented as ratio or as number and percentage and differences were compared using the Pearson chi-squared test.

Repeated-measures analysis of variance (ANOVA) was used to analyze serial measurements and to examine the effect of time, randomization group, and time-group interaction on the change in the outcome measures.

A p-value  $< 0.05$  was considered statistically significant.

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