
| **RESEARCH ARTICLE**

Effect of Exercise on Myocardial Ischemic-reperfusion Injury in Sprague- Dawley Rat Model

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| **ABSTRACT**

Globally, cardiovascular disease is the leading cause of death. Of all the spectra of cardiovascular ailments, myocardial infarction (MI) contributes the biggest proportion of mortality. MI results when blood flow to the myocardium is interrupted, thus, is routinely treated by reperfusion therapy, a strategy that may cause ischemic reperfusion injury. Presently, this injury lacks effective treatment measures; therefore, there is need for more investigation to devise its preventive measures. The current study sought to investigate the effect of varying intensities of exercise on myocardial ischemic reperfusion injury. Twenty male Sprague Dawley rats were divided into 4 groups (N = 5). Three of these were subjected to varying intensities of exercise 21 days. One group served as a control. Ischemia and reperfusion (I & R) procedure was performed on Langendorff perfused hearts and contractile function was recorded during the pre-ischemic and post ischemic periods. These recordings were then compared to assess the degree of myocardial recovery after I & R. Groups were compared using ANOVA ($\alpha=0.05$). Results showed that there were statistically significant differences between groups in left ventricular developed pressure ($P=0.04$), maximum rate of contraction ($P=0.036$), maximum rate of relaxation ($P=0.04$) and heart rate ($p=0.041$). Moderate intensity exercise may be having protective effects against ischemic reperfusion injury (IRI). This effect was demonstrated in the current study by improved recovery of left ventricular contractile function following myocardial ischemic-reperfusion injury in the group subjected to moderate intensity exercise.

| **KEYWORDS**

Exercise, Myocardial infarction, Ischemic reperfusion injury

| **ARTICLE INFORMATION**

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1. Introduction

Cardiovascular disease is a frequent cause of death worldwide. It is estimated to cause fifteen million deaths annually translating to 31 % of global mortality (Keates et al., 2017), with ischemic heart disease contributing to 13% of this (Keates et al., 2017). Myocardial infarction is the main spectrum of ischemic heart disease that contributes to this mortality, as it is estimated to account for 20% of global deaths (Ahmadi et al., 2015). In sub-Saharan Africa, cardiovascular disease accounts for 9.2% of total deaths and is the leading cause of death among the elderly (Jackson, 2011). Further, this disease contributes to 7-10% of all adults admitted to hospital in this region (Sliwa et al., 2010). Eighty percent of global deaths attributed to cardiovascular disease occur in low- and middle-income countries (Sliwa et al., 2010). In Kenya, ischemic heart disease account for 25% of all admissions and 13% of deaths with the biggest contributor being myocardial infarction (Vusirikala et al., 2019).

Myocardial infarction results from an imbalance between myocardial oxygen demand and supply. When demand exceeds supply, ischemic necrosis of the myocardium may ensue (Thygesen et al., 2018). Etiology of myocardial infarction is multifactorial but the most prevalent causal factor is occlusion of the coronary artery which leads to interruption of perfusion to the myocardium (Anand et al., 2008). This leaves reperfusion therapy as the preferred treatment option that can be explored. This, can be achieved either through per cutaneous coronary intervention (PCI) or use of thrombolytic agents (Barron et al., 1998). However, reperfusion therapy can cause reperfusion injury which inflicts additional damage to the infarcted myocardium. IRI has contributed immensely to the mortality from MI and the morbidity among the survivors of myocardial infarction and has significantly dampen the benefits of reperfusion therapy (Hausenloy et al., 2013). Up to date, there are no preferred curative strategy of IRI that have been documented. Therefore, it calls for more investigation to identify possible preventive measures for this condition. Further, a study to determine possible modifiable risk factors to IRI is indispensable. Adoption of preventive measures and elimination of modifiable risk factors to myocardial IRI will positively influence the outcome of reperfusion therapy among sufferers of MI.

2. Materials and Methods

The current study employed a laboratory-based, true experimental study design. Twenty male Sprague-Dawley rats, weighing between 250 and 300 g at the beginning of the experiment, were used. Prior to commencement of the experimental procedures, the animals were acclimatized to the laboratory environment and housed in standard rodent cages under controlled laboratory conditions. The rats had free access to standard approved rodent pellets and clean drinking water ad libitum throughout the acclimatization and experimental periods. Following acclimatization, the animals were randomly allocated into four experimental groups, with five rats per group (N = 5), as follows:

Normal control (NC):	Not subjected to exercise
Low intensity exercise (LIE):	Subjected to 2 minutes of exercise per day for 21 days
High intensity exercise (MIE):	Subjected to 5 minutes of exercise per day for 21 days
High intensity exercise (HIE):	Subjected to 10 minutes of exercise per day for 21 days

2.1 Experimental protocol

Exercise was achieved by subjecting the animals to a forced swim test. Glass cylinder was half filled with water and the animals in each of the treatment groups was placed in water for the specified duration. In the course of forced swim test, animals were observed for potential drowning.

After the treatment period, animals were administered with 7.5mg/kg of unfractionated heparin and sacrificed by using intraperitoneal injection of ketamine (100mg/kg) (Hiebert et al., 2008). Hearts were then harvested by making an incision on the anterior abdominal wall and then advancing to the thoracic cavity by excising the diaphragm. The sternum was then dissected from the xiphoid process upwards while care was observed not to damage the aorta. The aorta was then identified, held at the root and cut at a point just proximal the aortic arch. With the secured aorta, the entire heart was then excised out of the thoracic cavity and mounted by the aorta on the Langedorff isolated heart perfusion apparatus, to provide retrograde perfusion using Krebs Henseleit buffer solution. The perfusate flow rate was set at 8ml/min. A barometer was inserted into the left ventricle through the mitral valve to measure changes in the left ventricular pressure. After 15 minutes, perfusion was stopped for 30 minutes to induce global myocardial ischemia and thereafter resumed for another 30 minutes. Left ventricular developed pressure (LVDP), maximum rate of contraction (dp/dt_{max}), maximum rate of relaxation (dp/dt_{min}) and heart rate (HR) were measured five minutes before induction of ischemia and 20 minutes after reinstatement of perfusion and recorded using Lab chart pro software (Minasian et al., 2013). These parameters were used to assess the degree of myocardial recovery following ischemia and reperfusion by comparing the pre-ischemic and post-ischemic readings as percentage.

2.2 Statistical analysis

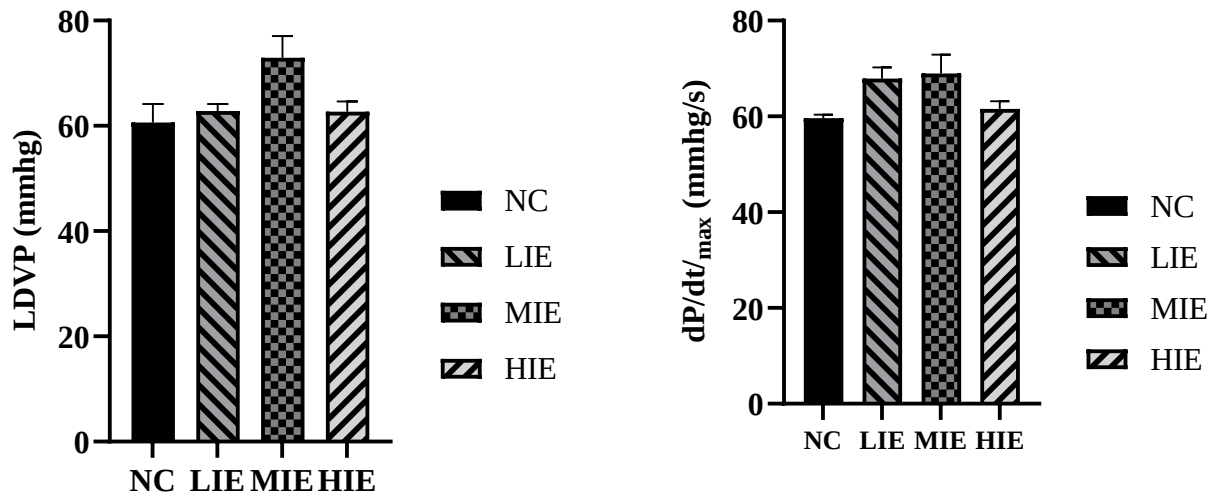
Data was collected using customized data acquisition tables and entered into GraphPad Prism (version 10) software for analysis. Shapiro Wilk's test and Levine's test were used to check for normality and homoscedasticity of data respectively. Groups were compared using one-way ANOVA where $P < 0.05$ was considered to be statistically significant. Post hoc statistical analysis by Tukey test was performed to identify groups with significant differences. Results are presented in bar charts as Means $\pm$ SEM presented.

2.3 Ethical consideration

Ethical conduct was observed at all times during the course of this study. FELASA guidelines were adhered to as the principles of Replacement, Reduction and Refinement were observed ^[12]. Ethical approval was sought from the institutional Research Ethics Committee.

3. Results

There were statistically significant differences between groups in recovery LVDP percentage recovery ($P=0.04$), $dP/dt_{\max}$ percentage recovery ($P=0.036$), $dP/dt_{\min}$ percentage recovery ($P=0.042$) and Heart rate recovery ($P=0.041$). Post hoc statistical analysis with Tukey revealed that there were statistically significant differences between MIE and NC, between MIE and LIE and between MIE and HIE in all the parameters measured. However, there were no statistically significant differences between NC and LIE, between NC and HIE, between and LIE and HIE in all the contractile indices assessed. The results are presented in Figure 1.



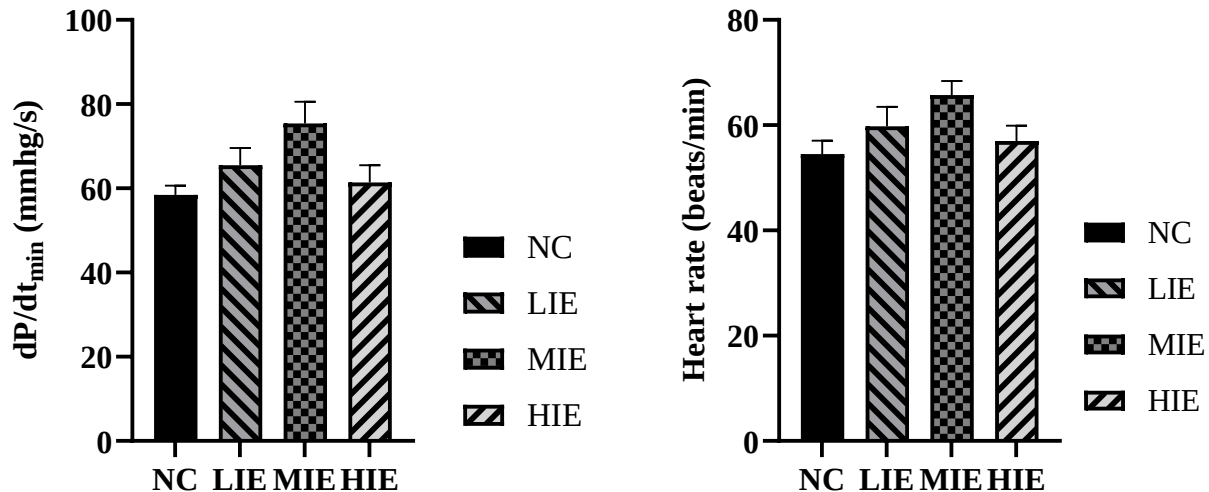


Figure 1: Effect of exercise intensity on cardiac functional parameters. Left ventricular developed pressure (LVDP), maximum rate of left ventricular pressure development (dP/dt_{max}), minimum rate of left ventricular pressure development (dP/dt_{min}), and heart rate in the normal control (NC), low-intensity exercise (LIE), moderate-intensity exercise (MIE), and high-intensity exercise (HIE) groups. Error bars represent standard deviation around the mean.

4. Discussion

In the current study, moderate intensity exercise possessed a protective effect against myocardial IRI as demonstrated by a statistically significant recovery of the left ventricular function in the treated groups. There were statistically significant differences between different groups in percentage recovery of LVDP heart rate, dP/dt_{max} . Preservation of LVDP, and dP/dt_{max} in the MIE group could mean that this group had more functional myocytes suggesting the potential prophylaxis against myocardial apoptosis and necrosis that occur in IRI (Chang et al., 2006). In addition, MIE may have prevented the occurrence of myocardial stunning, a pathology which would have impacted negatively on the myocardial contractile function (Duncker et al., 1998). It is probable that the intervention exerted these prophylactic actions by curbing accumulation of reactive oxygen species (ROS). This is because ROS are thought to cause apoptosis, necrosis and myocardial stunning during myocardial IRI (Tao et al., 2007). Better recovery of the dP/dt_{min} could imply that the cellular elements needed for myocardial relaxation were enhanced. For instance, increasing the action of Sarcoplasmic Reticulum-Calcium ATPase (SERCA) facilitates faster and more efficient re-uptake of calcium into the sarcoplasmic reticulum. This optimizes the ventricular diastolic function (Wu et al., 2001). Phospholamban, in its phosphorylated state increases the activity of SERCA. This protein is a potential target of destruction by oxidative stress in IRI. Therefore, MIE could have prevented this oxidative damage of phospholamban, leading to better SERCA activity and consequently improved dP/dt_{min} in this group (Periasamy et al., 2008; Babušíková et al., 2012; Yokoe et al., 2017). Preservation of heart rate in the MIE group meant that the integrity of sinus node was maintained (Pinnell, 2007). ROS generated in IRI may inappropriately inactivate ion channels (Zima, 2006). If slow sodium channels in the pacemaker cells are inactivated, rate of phase 4 depolarization of the pacemaker potential will be reduced, leading to a small number of action potential generated per unit time, and subsequently a reduction in heart rate (Monfredi et al., 2010). MIE may have dampened the oxidative inactivation of these sodium channels in the pacemaker cells, a factor that could explain the higher heart rate in the group that was subjected to this intensity of exercise.

5. Conclusion

The current study has demonstrated that MIE may be having protective effects against IRI in rats. This effect was demonstrated by preservation of left ventricular function following myocardial ischemic-reperfusion injury since the left ventricular pressure dynamics were improved in MIE group than negative control. The findings of the current hence give insight on the role of exercise as a preventive measure for myocardial IRI.

5.1 Study limitations

- Limited sample of cardiac outcomes: Cardioprotection was assessed mainly through functional parameters—LVDP, dP/dt_{max} , dP/dt_{min} and heart rate. The current study did not directly measure infarct size, myocardial histopathology, or cardiac biomarkers due to the nature of the experimental study. Thus, the cellular mechanism responsible for the apparent protection were inferred rather than directly measured.
- Ex vivo global ischemia model limits clinical generalizability: The hearts were isolated and subjected to 30 minutes of global ischemia followed by reperfusion. This model is useful for studying myocardial function but may not fully reproduce the pathophysiology of coronary artery occlusion and reperfusion in vivo.

5.2 Recommendations for future studies

- Investigate the molecular mechanisms of cardioprotection by measuring oxidative stress and antioxidant markers such as catalase, superoxide dismutase, glutathione and lipid peroxidation, together with molecular markers of apoptosis and mitochondrial function.
- Include direct measures of myocardial injury, such as infarct size, histopathological assessment, troponin, CK-MB and markers of apoptosis/necrosis.
- Use an in-vivo myocardial ischemia-reperfusion model in future work to establish whether the findings observed in isolated hearts translate to the whole animal.

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