## Original Article

# *Protective Effects of N-Acetyl Cysteine on Cardiac Function in Diabetic Patients Undergoing Coronary Artery Bypass Grafting*

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## ABSTRACT

***Background:*** The preservation of cardiac function in diabetic patients undergoing coronary artery bypass grafting (CABG) would result in improved prognoses in patients. Therefore, in this study, the protective effects of N-acetyl cysteine (NAC) on cardiac function in diabetic patients undergoing CABG were determined.

***Methods:*** This triple-blind, randomized, clinical trial study recruited 240 consecutive diabetic patients undergoing CABG in a referral tertiary health-care center, Hamadan, Iran. The patients were randomly assigned (simple random sampling) to receive either NAC or a placebo. In both groups, ischemic preconditioning was developed with a manometer cuff around the arm. The cuff was filled up to 200 mm Hg for 5 minutes before it was emptied to 0 mm Hg for 5 minutes. This technique was repeated 3 times.

***Results:*** The mean preoperative ejection fraction (EF) and the preoperative myocardial performance index (MPI) were the same in the 2 groups ($P$>0.05). The postoperative EF and the MPI were not significantly different between the 2 groups ($P$>0.05). The trend of changes in the EF and the MPI was not different between the groups ($P$>0.05).

***Conclusions:*** This study demonstrated that NAC in the ischemic preconditioning method did not create a significant effect compared with a placebo, which is in congruence with previous studies in animal models. ***(Iranian Heart Journal 2021; 22(2): 96-100)***

**KEYWORDS:** N-acetyl cysteine, Cardiac function, Coronary artery bypass, Diabetic patients, Preconditioning

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Cardiovascular disorders are the main cause of morbidity and mortality worldwide. [1, 2] Coronary artery bypass grafting (CABG) is one of the most important therapeutic modalities in patients with critical coronary stenosis and subsequent myocardial infarction. [3, 4] However, some adverse events may be developed in patients undergoing CABG due to some technical difficulties. [5-7] Therefore,

it is necessary to develop new methods to decrease the injury and improve the prognosis, especially with further focuses on anesthetic interventions. [8, 9]

One of the established methods for improving surgical outcomes after CABG is ischemic preconditioning (IPC) or ischemia-reperfusion injury before and during surgery as an experimental modality to develop resistance to blood loss and thus oxygen requirements. [10, 11] Accordingly, in this method, nonlethal short periods of ischemia are imposed on myocardial cells. [11] This mechanism is abnormal in hyperglycemic states. [12] It should be noted that diabetes is a contributing and aggravating factor for prognosis in patients under CABG. [13, 14] N-acetyl cysteine (NAC) is a proposed therapeutic without established effects in this era. NAC is an antioxidant and anti-inflammatory and can reduce cellular oxidative damage and systemic inflammation during cardiac surgery. [15]

Given the high risk of anesthesia in diabetic patients for CABG and the need for improved surgical conditions for these patients, in this study, the protective effects of NAC on cardiac function in diabetic patients undergoing CABG were determined.

## METHODS

This triple-blind, randomized clinical trial recruited 240 consecutive diabetic patients undergoing CABG in a referral tertiary health-care center, Hamadan, Iran. The patients were randomly assigned (simple random sampling) to receive either NAC or a placebo. In both groups, IPC was developed with a manometer cuff around the arm. The cuff was filled up to 200 mm Hg for 5 minutes and then emptied to 0 mm Hg for 5 minutes. This technique was repeated 3 times. The study protocol was approved by the institutional ethics committee (IRCT with the code of IR.UMSHA.REC.1396.77).

The inclusion criteria were the male gender (female patients have unreliable responses to percutaneous coronary intervention), diabetes mellitus, age range from 45 to 75 years, myocardial ischemia candidated for CABG, and a minimal cardiac index over 2.5 lit/m$^2$. The exclusion criteria were requests to quit, death, myocardial infarction after CABG, intermediate severity valvular disorders, long-term use of inotropic agents before or after surgery, and arm circumferences greater than the manometer cuff (impossibility of IPC).

In both groups, transthoracic echocardiography was done before CABG and 3 days afterward to determine the cardiac output and the myocardial performance index (MPI). Between-group randomization was done by a blinded operator. The intervention group received a single intravenous dose of NAC (50 mg/kg), while the control group was administered the same volume of normal saline as a placebo by the blind operator. Echocardiography was done by a blinded cardiologist. Changes in the ejection fraction (EF) and the left ventricular MPI were determined and compared between the 2 groups by a blinded statistical analyzer.

Data analysis was performed among 240 subjects, consisting of 120 subjects in the control group and 120 patients in the intervention group. All the data analyses were conducted with SPSS, version 19.0 (Statistical Procedures for Social Sciences; Chicago, Illinois, USA). The independent-sample-*t* test was used, and a *P* value of less than 0.05 was considered statistically significant.

## RESULTS

In this study, all the patients were male. The mean age was 58.4±11.7 years in the NAC group and 55.7±9.9 years in the control group ($P>0.05$). According to the independent-sample-*t* test results (Table 1),

the mean body mass index, the preoperative EF, and the preoperative MPI were the same in the groups ($P$>0.05). Additionally, the postoperative EF and MPI were not significantly different between the 2 groups ($P$>0.05).

**Table 1:** Data regarding the 2 study groups

| | Group | Mean | SD | *P* value |
|---|---|---|---|---|
| BMI | NAC | 25.4301 | 1.83540 | 0.565 |
| | Control | 25.5879 | 2.37046 | |
| Preoperative EF | NAC | 42.0417 | 4.51402 | 0.651 |
| | Control | 42.3333 | 5.42068 | |
| Postoperative EF | NAC | 42.6667 | 4.14715 | 0.377 |
| | Control | 43.2083 | 5.25788 | |
| Preoperative MPI | NAC | 0.5742 | 0.09569 | 0.137 |
| | Control | 0.5918 | 0.08576 | |
| Postoperative MPI | NAC | 0.6429 | 0.09570 | 0.809 |
| | Control | 0.6458 | 0.09147 | |

NAC, N-acetyl cysteine; BMI, Body mass index; EF, Ejection fraction; MPI, Myocardial performance index

As is demonstrated in Table 2, changes in the EF and the MPI were not different between the 2 study groups ($P$>0.05).

**Table 2:** Changes in the EF and the MPI in the NAC and control groups

| | Group | Mean | SD | *P* value |
|---|---|---|---|---|
| EF Change | NAC | 0.6250 | 2.47360 | 0.464 |
| | Control | 0.8750 | 2.80025 | |
| MPI Change | NAC | 0.0682 | 0.06870 | 0.079 |
| | Control | 0.0541 | 0.05453 | |

NAC, N-acetyl cysteine; EF, Ejection fraction; MPI, Myocardial performance index

## DISCUSSION

In this study, we evaluated the efficacy of NAC in IPC among diabetic patients undergoing CABG and found that NAC had no effects on our patients with diabetes (Table 1, Table 2, and Fig. 1 & 2).

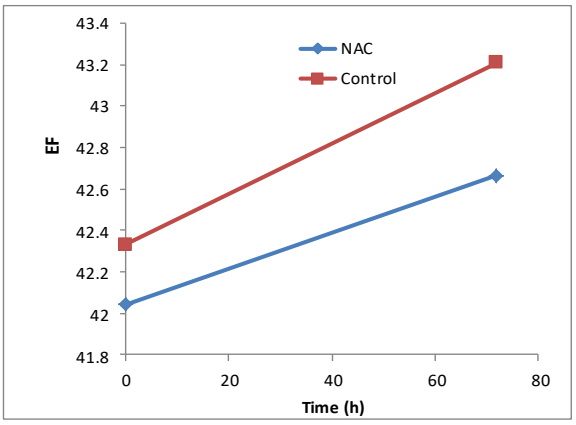


**Figure 1:** The image illustrates over-time changes in the ejection fraction.

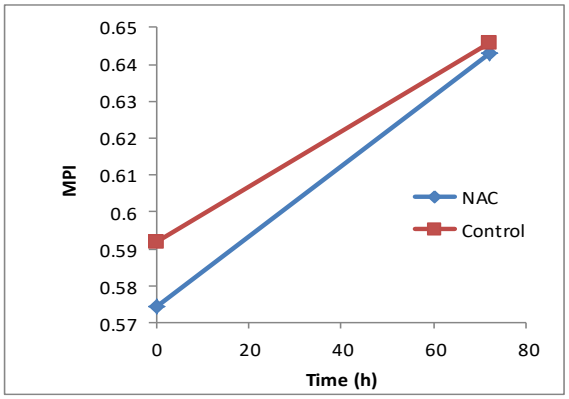


**Figure 2:** The image depicts over-time changes in the myocardial performance index.

IPC fails to create the desired response in patients with abnormal glycemic status. The contributing mechanism for NAC is the anti-inflammatory effect. In a preliminary evaluation of the use of NAC in patients undergoing CABG by Eren et al, [16] pulmonary parameters were compared between groups with and without NAC. The results showed that the A-a oxygen gradient was better in the patients receiving NAC than in those receiving a placebo. Nonetheless, that study was performed on nondiabetic subjects. Vento et al [17] demonstrated improved capacity to resist oxidative stress according to myeloperoxidase and glutathione levels.

Sucu et al [18] showed that the use of NAC 3 days before surgery for the reduction of

oxidative effects due to pump in patients undergoing CABG decreased the level of interleukin-6 within hours after surgery compared with the control group. Orhan et al [19] demonstrated that the use of intravenous NAC in CABG patients decreased the levels of tumor necrosis factor in myocardial cell biopsies. EI-Hammsy et al [20] reported that adverse clinical outcomes such as arrhythmias, death, myocardial infarction, transfusion need, and intensive care unit admission, as well as laboratory parameters such as the levels of troponin, hemoglobin, platelet, creatinine, and CK-MB, were similar in their study groups.
Peker et al [21] assessed 40 patients divided into NAC and placebo groups undergoing CABG and reported no difference between the groups in terms of the CK-MB level. Kurian et al [22] assessed lipid peroxidation levels in patients who received NAC and magnesium before aortic clamping during CABG and found low peroxidation levels accompanied by improved erythrocyte ATPase and inflammatory markers in the case group by comparison with the placebo group.

## CONCLUSIONS

The present study assessed the protective effects of NAC on cardiac function in diabetic patients undergoing CABG. The results showed that NAC in the IPC method failed to create a significant effect by comparison with a placebo, which is in congruence with previous studies in animal models. However, further studies are required to attain more definite results, especially with the use of some other useful therapeutics for the IPC method.

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