

# A comparative study of interleukin 6 and 17 serum levels in patients undergoing coronary artery bypass surgery using off-pump and on-pump methods

Kambiz Alizadeh<sup>1</sup>, Atefeh Hosseinpour<sup>2</sup>, Masoomeh Tabari<sup>\*3</sup>, Majid Rajabian Noghondar<sup>4</sup>, Negar Morovatdar<sup>5</sup>, Azra Izanloo<sup>6</sup>

<sup>1</sup> Department of Cardiovascular Surgery, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

<sup>2</sup> Department of Biology, Faculty of Science, Payam-e Noor University of Mashhad, Mashhad, Iran

<sup>3</sup> Department of anesthesiology, Faculty of medicine, Mashhad University of medical sciences, Mashhad, Iran

<sup>4</sup> Department of Biology, Faculty of Science, Payam-e Noor University, Tehran, Iran

<sup>5</sup> Clinical Research Development Unit, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>6</sup> Razavi Cancer Research Center, Razavi Hospital, Imam Reza International University, Mashhad, Iran

\* **Corresponding authors:** Masoomeh Tabari, MD. Department of Anesthesiology, Mashhad University of medical sciences, Mashhad, Iran. Ghaem Hospital, Ahmadabad Street, Mashhad, Iran. Fax: +5138417402, Post-code: 99199-91766. E -mail: tabarim@mums.ac.ir

Received 2020 November 18 Accepted 2020 November 24

## Abstract

**Introduction:** This study aims to investigate the role of coronary artery bypass graft (CABG) surgery by off-pump and on-pump methods in the severity of postoperative inflammation based on serum levels of interleukin 6 (IL6) and interleukin 17 (IL17).

**Methods:** This is a cross-sectional study in which 39 patients' candidate for CABG were evaluated in terms of serum levels of IL17 and IL6 before and after surgery in two groups of off-pump and on-pump CABG.

**Results:** Thirty-nine patients with an average age of  $63 \pm 8.9$  in the on-pump group and  $59 \pm 7.74$  in the off-pump group were evaluated. There was no significant difference between the two groups in terms of baseline information and underlying diseases. IL6 serum level ( $p=0.249$ ) was not significantly difference between the two groups. However, IL17 serum level ( $p=0.012$ ) demonstrated a significant difference between the two groups.

**Conclusion:** In general, the results of this study showed that increased IL6 serum level following coronary artery bypass was not different between the two methods of CABG surgery. Besides, IL17 exhibited a significant difference between the two groups that it was reduced in on-pump group after surgery. It can be due to special condition's patients or low sample size of study. Moreover, the postoperative complications were not significantly different between the two groups. This valuable outcome contradicts the popular belief that the use of the CARDIO PULMONARY BYPASS (CPB) system stimulates the immune system and hence its application should be limited.

**Keywords:** Off-pump, On-pump, Interleukin, CABG

## 1. Introduction

Inflammation is a major complication ensuring coronary artery bypass graft surgery (CABG). On-pump CAB, due to its safety, positive effect and low mortality, is the standard surgery for transmyocardial laser revascularization. (1) However, on-pump CAB can bring about some undesirable side effects such as inflammation. To reduce the inflammation caused by surgery and improve clinical outcomes, off-pump CAB has been recommended in which the surgeon sutures the blood vessels while the heart is still beating. The main advantage of off-pump surgery is decreased surgical time, costs and complications compared

to the on-pump method. (2) The results of a meta-analysis have shown that off-pump surgery can reduce the risk of postoperative strokes. (3) However, off-pump surgery is challenging and requires advanced surgical skills. On the other hand, although the benefits of off-pump surgery are obvious and it has been shown to alleviate the effects of postoperative inflammation. (4-5), other studies have reported conflicting results. (6-7)

Interleukins (ILs) are a class of cytokines produced by leukocytes. (8) It has been shown that interleukins play a key role in a number of immune and inflammatory responses. (9-10) Interleukins 6 (IL-6) is an anti-

inflammatory cytokine that plays a pivotal role in inducing acute phase reactions and controlling acute local and systemic inflammatory response. (11)

Interleukins 17 (IL17) is a hemodynamic molecule that appears in both glycosylated and non-glycosylated forms. The effect of this cytokine is probably attributable to its glycosylated form. The human IL-17 gene is located on the long arm of chromosome 2. IL-17 affects estrogen cells, forcing them to produce cytokines such as IL-6 and C-CSF, which leads to the production of neutrophils. (12) IL17 is a cytokine that acts as a potent mediator in delayed reactions by improving the production of chemokines in different tissues in order to absorb monocytes and neutrophils in the inflammation site, which is similar to IFN- $\gamma$ . IL17 is produced by adjuvant cells and induces destructive tissue damage in delayed-type reactions. It also acts as an anti-inflammatory cytokine that responds to attacks on the immune system by extracellular pathogens and destroys the cellular pathogen. (13)

The goal of this study is to investigate the role of CABG by off-pump and on-pump methods in the severity of postoperative inflammation based on IL 6 and 17.

## Methods

This is a cross-sectional study. The study population consists of 39 patients candidate for CABG surgery who referred to a public hospital over a six-month period. Patients who were scheduled for emergency surgery or had a history of autoimmune and inflammatory diseases, patients treated with corticosteroids or immunosuppressive drugs, patients with a history of cardiac arrhythmias and CPR during surgery, patients undergoing off-pump surgery where certain conditions had necessitated a shift to on-pump method, patients with a history of advanced renal and hepatic insufficiency, cancer, severe allergies, or

concomitant valvular disease, and finally patients who did not wish to participate in the study were excluded.

After the informed consent forms were obtained from the patients, we recorded their demographic and clinical data. The patients were then randomly assigned to two groups of on-pump and off-pump surgeries, and a skilled heart surgeon conducted the operation.

2 cc of the patients' blood was taken before and after surgery to measure serum IL6 and IL17 levels. It was sent to the laboratory in less than 30 min, and the patients' serum was isolated after 10-min centrifugation at 2000-3000 RPM. The hemolytic or lipomic samples were excluded.

To measure serum levels of IL 6 and 17, the sandwich analysis method was used. IL 6 was evaluated by Diaclone kit in the detection range of 25.6-200 pg/ml, with a cut-off of 2 pg/ml and high specificity and ZellBio kit were used to evaluate the level of IL17.

The present study was approved by the ethics committee of Mashhad University of Medical Sciences.

## Statistical analysis

The data analysis was conducted by SPSS software. Qualitative variables with high frequency and quantitative variables with low mean and standard deviation were described. Also, the possible relationship between each background variable and the main variables was investigated using the independent t-test, covariance test and paired t-test. In all computations, a significance level of  $p < 0.05$  was considered.

## Results

The study was performed on 39 patients, 19 of whom underwent off-pump surgery and 20 had on-pump surgery. The demographic information of participants is reported in Table 1.

**Table 1.** Demographic characteristics of the study population and their frequency

	On-pump	Off-pump	Level of significance
Sex (male)	14 (70%)	10 (52.6%)	0.26
Age	63±8.9	59±7.74	0.096
Weight	71±13.38	69±13/02	0.7
Height	164±12/05	164±8/62	0.98
Hypertension	15(75%)	15(78.9%)	0.77
Diabetes	8 (40%)	9 (47.4%)	0.64
Chronic obstructive pulmonary disease	0 (0%)	1 (5.3%)	0.29
Hyperlipidemia	10 (50%)	6 (31.6%)	0.24
Drugs addiction	5 (25%)	9 (47.4%)	0.14
History of thyroid disease	1 (5%)	0 (0%)	0.32
Preoperative hemoglobin level	2.1±13.51	2.22±12.92	0.5
PH changes in venous blood before surgery	0.052±7.39	0.038± 7.41	0.359

As can be seen, there is no significant difference between the two groups in terms of characteristics and clinical conditions at the baseline.

In the on-pump group, 55% of patients had an EF of 20-50% and 45% had an EF of above 50%. In the off-pump group, 26% of patients had an EF of 20-50% and 74% had an EF of above 50%. There was no significant difference between the two groups in this regard. (P=0.06)

In most patients in the on-pump group (51%), three blocked vessels were detected in the angiogram, but in the off-pump group, only 38% had three blocked vessels. There was no significant difference between the two groups in this respect. (P = 0.09)

There was, however, a significant difference between the two groups in terms of the number of grafts during surgery. (P = 0.04) In the on-pump group, most patients

(85%) had 3 or 4 grafts during the surgery. In the off-pump group, 53% of patients had 3 or 4 grafts and 47% had one or two grafts during the operation.

There was no significant difference between the two groups in terms of postoperative hemoglobin levels. (p = 0.473)

The results of the covariance test showed that IL6 was not significantly different between the two groups after surgery. (p=0.462), but IL17 exhibited a significant difference between the two groups. (p = 0.012)

The changes in IL 6 and 17 are shown in Table 2.

The mean changes of IL 6 in the two groups of opium users and non-opium users manifested a significant difference. (p = 0.016) However, the mean changes of IL 17 in the two groups of opium users and non-opium users was not significantly different. (p = 0.114).

**Table 2.** Average changes of IL 6 and 17 in two on-pump and off-pump groups

	IL-6 before CABG	IL-6 after CABG	IL-17 before CABG	IL-17 after CABG
(Mean±SD) On-pump group	3.87±7.54	50.70±34.81	8.73±13.28	6.76± 4.02
(Mean±SD) Off-pump group	1.29±2.39	37.63± 27.16	3.38± 2.73	3.53± 2.56

## Discussion

Off-pump CAB have a number of advantages such as reduced operating time and cost over on-pump CAB surgery. (2) However, there are controversies whether off-pump surgery can significantly reduce postoperative inflammation. In the present study, no significant difference was observed between the two groups in terms of the serum level of IL 6 but the two groups were significantly different in terms of IL 17 serum level (p = 0.012). However, in the off-pump group, we observed that this value increased by 0.2. Since the difference between IL 17 levels before and after surgery was not significant in the off-pump group (p = 0.846), this difference could be attributed to small sample size of the study. Hence, it is often argued that IL 17 is not a good factor for evaluating the inflammatory response after CABG.

In line with the present study, the 2017 meta-analysis conducted by Meng et al. did not show any significant difference in the serum IL 6 and 8 serum levels in the two groups of off-pump and on-pump surgeries. This means that off-pump CAB surgery does not have any advantages over on-pump CAB surgery in reducing postoperative inflammatory response in patients. (1)

Shi et al. (14) found that IL 6 could induce an inflammatory response associated with obesity. In addition, some anti-inflammatory markers, including IL-6, were positively linked to obesity-independent insulin resistance and

metabolic syndrome features. (15-17) In the present study, patients in the two groups were not significantly different at the baseline in terms of obesity and diabetes.

In the same vein, the results of another 2011 study did not reveal any significant association between IL 6 polymorphism and postoperative CABG complications in the two groups both with and without postoperative complications. (10) This study is somewhat consistent with the results of our study, the only difference is that they did not draw a distinction between the two surgical methods.

One of the limitations of the present study was its small sample size. Therefore, it is recommended to undertake more large-scale and multicenter trials to address this drawback. Opium may appear to be a confounding factor as it suppresses the secretion of anti-inflammatory cytokines and constrains the stimulation of the inflammatory system compared to other patients.

## Conclusion

In general, the results of this study showed that increased IL6 serum level following coronary artery bypass was not different between the two methods of CABG surgery. Besides, IL17 exhibited a significant difference between the two groups that it was reduced in on-pump group after surgery. It can be due to special condition's patients or low sample size of study. Moreover, the postoperative

complications were not significantly different between the two groups. This valuable outcome contradicts the popular belief that the use of the CARDIO PULMONARY BYPASS (CPB) system stimulates the immune system and hence its application should be limited. However, for definite conclusions to be drawn, more large-scale studies, especially multi-center trials are needed. The present study reaffirmed that the off-pump method does not increase inflammation after surgery.

## References

- Meng F, Ma J, Wang W, Lin B. Meta-analysis of interleukin 6, 8, and 10 between off-pump and on-pump coronary artery bypass groups. *Bosn J Basic Med Sci*. 2017 May; 17(2): 85–94. doi: 10.17305/bjbm.2017.1505
- Brinkman WT, Squiers JJ, Covington KR, Wheeler DA, Arsalan M, Smith RL, et al. Mini-extracorporeal circulation and off-pump techniques associated with less inflammatory gene expression as compared to on-pump in the 24-hour postoperative window following coronary artery bypass grafting. *J Cardiothorac Surg* 2015;10(Suppl 1): A101. doi: 10.1186/1749-8090-10-S1-A101
- Afilalo J, Rasti M, Ohayon SM, Shimony A, Eisenberg MJ. Off-pump vs. On-pump coronary artery bypass surgery: An updated meta-analysis and meta-regression of randomized trials. *Eur Heart J* 2012;33(10):1257-67. Doi: 10.1093/eurheartj/ehr307.
- Nesher N, Frolkis I, Vardi M, Sheinberg N, Bakir I, Caselman F, et al. Higher levels of serum cytokines and myocardial tissue markers during on-pump versus off-pump coronary artery bypass surgery. *J Card Surg* 2006;21(4):395-402. doi:10.1111/j.1540-8191.2006.00272.x.
- Wan IY, Arifi AA, Wan S, Yip JH, Sihoe AD, Thung KH, et al. Beating heart revascularization with or without cardiopulmonary bypass: Evaluation of inflammatory response in a prospective randomized study. *J Thorac Cardiovasc Surg* 2004;127(6):1624-31. doi: 10.1016/j.jtcvs.2003.10.043.
- Ghorbel MT, Cherif M, Mokhtari A, Bruno VD, Caputo M, Angelini GD. Off-pump coronary artery bypass surgery is associated with fewer gene expression changes in the human myocardium in comparison with on-pump surgery. *Physiol Genomics* 2010;42(1):67-75. doi: 10.1152/physiolgenomics.00174.2009.
- Rogers CA, Pike K, Angelini GD, Reeves BC, Glauber M, Ferrarini M, et al. An open randomized controlled trial of median sternotomy versus anterolateral left thoracotomy on morbidity and health care resource use in patients having off-pump coronary artery bypass surgery: The Sternotomy Versus Thoracotomy (STET) trial. *J Thorac Cardiovasc Surg* 2013;146(2):306-16.e9. DOI: 10.1016/j.jtcvs.2012.04.020.
- Brocker C, Thompson D, Matsumoto A, Nebert DW, Vasiliou V. Evolutionary divergence and functions of the human interleukin (IL) gene family. *Hum Genomics* 2010;5(1):30-55. doi: 10.1186/1479-7364-5-1-30.
- Cua DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, Seymour B, et al. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature* 2003;421(6924):744-8. doi: 10.1038/nature01355.
- Kuilman T, Michaloglou C, Vredeveld LC, Douma S, van Doorn R, Desmet CJ, et al. Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. *Cell* 2008;133(6):1019-31. Doi:10.1016/j.cell.2008.03.039.
- Xing Z, Gauldie J, Cox G, Baumann H, Jordana M, Lei XF, et al. IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses. *J Clin Invest* 1998;101(2):311-20. doi: 10.1172/JCI1368.
- Andrew H, Lichtman, Shiv Pillai. **Cellular and Molecular Immunology**. Abul Abbas. Translators: Talibzadeh A, Bajan M, and Khalili A. Tehran: Khalili Publications, 2012. (Persian)
- Vajgani M. **Immunology**. Tehran: Tehran University Jihad Organization Publications, 2016. (Persian)
- Shi C, Zhu L, Chen X, Gu N, Chen L, Zhu L, et al. IL-6 and TNF- $\alpha$  induced obesity-related inflammatory response through transcriptional regulation of miR-146b. *J Interferon Cytokine Res*, 2014;34(5):342-5. doi: 10.1089/jir.2013.0078.
- Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: Association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia* 1997;40(11):1286-92. doi: 10.1007/s001250050822.
- Phillips CM, Perry IJ. Does inflammation determine metabolic health status in obese and nonobese adults? *J Clin Endocrinol Metab* 2013;98(10):E1610-9. doi:10.1210/jc.2013-2038.
- Vozarova B, Weyer C, Lindsay RS, Pratley RE, Bogardus C, Tataranni PA. High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of Type 2 diabetes. *Diabetes* 2002;51(2):455-61. doi:10.2337/diabetes.51.2.455.