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Non-extracorporeal circulation for coronary artery bypass graft surgery is more beneficial than extracorporeal circulation

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Abstract. – OBJECTIVE: The objective of this study was to compare coronary artery bypass graft (CABG) surgery with non-extracorporeal vs. extracorporeal circulation. The study outcomes included operative time, number of graft vessels, pulmonary infection rates, and systemic inflammatory markers.

PATIENTS AND METHODS: 96 patients received selective CABG, either with non-extracorporeal (study group; n = 48) or extracorporeal circulation (control group; n = 48). Operative time, pulmonary infection rates, and blood levels of inflammatory markers TNF-α, IL-6, and IL-8 before and 4, 24, and 48 hours after the surgery were quantified. Graft vessels were quantified using computed tomography.

RESULTS: Operative time was significantly shorter in study group (4.58 ± 0.91 vs. 5.36 ± 1.12 hours in control group; $p < 0.05$). The number of graft vessels and pulmonary infection rates were comparable between both techniques. However, systemic inflammatory markers were significantly ($p < 0.05$) lower in study group at 4 and, partly, 24 hours after the surgery.

CONCLUSIONS: Extracorporeal circulation prolongs operation and can aggravate systemic inflammatory response. Therefore, CABG with non-extracorporeal circulation offers more beneficial outcomes.

Key Words:
Pulmonary infection, Inflammation, markers, Non-extracorporeal circulation, Extracorporeal circulation, Coronary artery bypass grafting.

Introduction

The morbidity due to coronary heart disease has markedly increased in recent years[1-3]. One of the treatment options for coronary heart disease is the coronary artery bypass grafting (CABG)[4-6]. CABG with non-extracorporeal circulation can avoid the injury associated with conventional CABG, which could be beneficial to protect cardiopulmonary function, decrease the prevalence of brain, lung and kidney complications, and minimize arrhythmias. Thus, CABG with non-extracorporeal circulation has been an effective and safe minimally invasive intervention for coronary heart disease[7-10]. However, CABG with extracorporeal circulation still remains the main therapeutic method for heart surgery. Little is known about postoperative pulmonary infection rates and systemic inflammatory response on CABG when non-extracorporeal circulation is used, especially when compared with extracorporeal circulation.

To address this knowledge gap, here we compared outcomes of CABG with non-extracorporeal vs. extracorporeal circulation. As treatment outcomes, operative time, number of graft vessels, pulmonary infection rates, and levels systemic inflammatory markers were analysed.

Patients and Methods

Patients

The study participants were 96 patients who received selective CABG in The People's Hospital of Laiwu City, The Affiliated Hospital of Qingdao University, Changhai Hospital, and The People's Hospital of Laicheng District in Laiwu City between October, 2012, and August, 2013, and were then transferred into intensive care units. The patients were divided into two groups that were respectively subjected to the different

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surgical methods. Patients who received CABG with non-extracorporeal circulation comprised study group (n = 48; 32 male and 16 female patients), while patients who received CABG under extracorporeal circulation comprised control group (n = 48; 34 male and 14 female patients). The patient age ranged from 36-66 years, with average ages being comparable between study and control groups (respectively, [mean ± SD] 54.92 ± 5.17 vs. 56.23 ± 4.56 years).

Exclusion criteria were (1) preoperative pulmonary disease, (2) fever, (3) liver or kidney disease, (4) treatment with calcium channel blockers, non-steroidal anti-inflammatory analgesic, or glucocorticoids within 2 weeks before the surgery, (5) need for other surgeries (e.g., resection of ventricular aneurysm, cardiac valve replacement, etc), and (6) positive inflammatory markers (e.g., positive antistreptolysin O test).

The study protocol was approved by the Ethics Committee. All patients were informed about the advantages and disadvantages of the treatment. Then, the patients gave informed consents to participate in the study.

Operation Technique

Median sternotomy was used in all patients. Patients in study group were connected to extracorporeal circulation machine (SC III type artificial heart-lung machine; Berlin, Germany), which was prepared without priming. During the surgery, different coronary artery branches were exposed according to the position, and 1.0 mg/kg heparin for semi-heparinization was given after completing the internal mammary artery separation. The activated clotting time was maintained at more than 250 sec. Conventional extracorporeal circulation was established in control group, with high-potassium cold crystalloid cardioplegic solution for bridge irrigation to protect the myocardium. The rolling axial flow pump and membrane oxygenator were used. First, the distal coronary artery was anastomosed. Then, the anastomosis of the side end was completed with an aortic sidewall forceps after declamping aorta.

After surgeries were completed, protamine was used to neutralize heparin at a 1:1.3 ratio. Patients were then transferred to the intensive care units for further treatment after surgery.

Study Outcomes

We recorded operative time and number of graft vessels. Graft vessels were quantified by computed tomography.

In addition to the above, blood specimens were collected at 4 time points (before and 4, 24, and 48 hours after the surgery). Two ml of fasting venous blood samples were collected in the morning at the above time points and centrifuged to obtain serum. As inflammatory markers, tumor necrosis factor (TNF)-α, interleukin (IL)-8, and IL-6 were quantified by respective ELISAs (Wuhan Boster Biological Engineering Co., Ltd, Wuhan, China).

Finally, we assessed the rates of pulmonary infections. To detect the pathogens, sputum samples were collected in sterile containers and immediately sent for microbiology and virology analyses. The pathogens were detected according to the guidelines of the Clinical and Laboratory Standards Institute.

Statistical Analysis

The SPSS version 19.0 (International Business Machines Corporation, Beijing, China) was used to analyze the study's findings. Quantitative data were presented as mean ± SD, and differences were compared using the *t* test. Qualitative data were presented as absolute numbers and proportion of positive cases. The p value of < 0.05 was considered as significantly significant.

Results

Operative Time and Number of Graft Vessels

Operative time was significantly shorter in study group (4.58 ± 0.91 vs. 5.36 ± 1.12 hours in control group; $p < 0.05$, Table I). However, the number of graft vessels was comparable between study and control groups (Table I).

Systemic Inflammatory Markers

The levels of TNF-α, IL-6, and IL-8 did not statistically differ between study and control groups before the surgery. The levels of these markers increased significantly during the early hours after the surgery and fell back to normal levels at later time points (Table II). Specifically, the levels of TNF-α and IL-6 were significantly higher at 4 and 24 hours after the surgery in both study and control groups ($p < 0.05$ vs. before the surgery, all comparisons; Table II), and normalized at 48 hours after the surgery. IL-8 showed a more short-lived surge in blood levels, with only the levels at 4 hours after the surgery being significantly different to pre-surgery levels (Table II).

Table I. Operative time and number of graft vessels.

Groups	Patients, number	Operative time, hours	Number of graft vessels
Study group (GABG with non-extracorporeal circulation)	48	4.58 ± 0.91*	3.01 ± 0.62
Control group (CABG with extracorporeal circulation)	48	5.36 ± 1.12	3.74 ± 0.76

Footnote: Data are presented as mean ± SD. *$p < 0.05$ vs. CABG with extracorporeal circulation.

Importantly, all tested markers were markedly higher in control patients ($p < 0.05$; Table II).

Prevalence of Pulmonary Pathogens

Among patients of study group, there were 6 patients with virus infections, 2 patients with infections with gram positive bacteria, and 10 patients with detected Gram negative bacteria (Table III). Patients of control group showed comparable rates of pulmonary infections: 10 patients with virus infections, 6 patients with infections with gram positive bacteria, 2 patients with *Mycobacteria tuberculosis*, 6 patients with detected gram negative bacteria, and 2 patients with co-infections (Table III).

Discussion

Many studies demonstrated that extracorporeal circulation causes systemic inflammatory response manifested by up-regulated systemic levels of TNF-α, IL-8, and IL-6, with negative implications for the body (myocardial depression, cognitive disorder, ischemia-reperfusion injury, capillary leak syndrome, etc)[11-17]. In contrast, in CABG with non-extracorporeal circulation, these adverse reactions are avoidable[18,19].

TNF-α, IL-8 and IL-6 are important modulators of immunity and inflammatory response[13 20 21]. Specifically, TNF-α, IL-8, and IL-6 ignite systemic inflammation, as reflected by the severity of systemic inflammatory response[14,22,23]. TNF-α is closely associated with activation of many inflammatory cells[24]. IL-8 exerts chemotactic effects on T basophil granulocytes, T lymphocytes, and neutrophils[13]. IL-6 modulates activity of B cells, T cells, hepatic cells, and macrophages[25]. In our study, systemic levels of the above inflammatory markers were significantly lower in patients undergoing CABG under non-extracorpo-

Table II. Systemic inflammatory markers before and after the surgery.

Inflammatory factor	Groups	Before the surgery	After the surgery		
			4 hours	24 hours	48 hours
TNF-α, ng/ml	Study group (CABG under non-extracorporeal circulation)	8.1 ± 4.2	12.5 ± 7.4* #	12.8 ± 5.9*,#	9.8 ± 4.2#
	Control group (CCABG under extracorporeal circulation)	8.4 ± 5.3	47.2 ± 20.1	31.6 ± 10.8	17.5 ± 6.9
IL-8, ng/ml	Study group (CABG under non-extracorporeal circulation)	73.8 ± 12.8	95.1 ± 27.8*,#	77.1 ± 35.2#	68.2 ± 16.5#
	Control group (CCABG under extracorporeal circulation)	76.5 ± 24.7	147.4 ± 57.6	107.1 ± 60.3	88.1 ± 23.7
IL-6, ng/ml	Study group (CABG under non-extracorporeal circulation)	10.8 ± 25.7	27.3 ± 69.9* #	16.1 ± 109.1* #	14.3 ± 26.9#
	Control group (CCABG under extracorporeal circulation)	10.4 ± 35.4	48.5 ± 129.4*	38.2 ± 48.2*	17.1 ± 30.5*

Footnote: Data are presented as mean ± SD. *$p < 0.05$ vs. before the surgery; #$p < 0.05$ vs. control group.

Table III. Detection of pulmonary pathogens after the surgery.

Pathogen	Study group (CABG under non-extracorporeal circulation)	Study group (CABG under extracorporeal circulation)
Viruses		
Cytomegalovirus	4 (8.33)	8 (16.67)
Influenza A virus	2 (4.17)	2 (4.17)
Gram positive bacteria		
Staphylococcus aureus	2 (4.17)	4 (8.33)
Coagulase-negative staphylococcus	0 (0)	2 (4.17)
Mycobacterium tuberculosis	0 (0)	2 (4.17)
Gram negative bacteria		
Pseudomonas aeruginosa	6 (23.5)	4 (8.33)
Klebsiella pneumoniae	2 (4.17)	2 (4.17)
Alcaligenes xylosoxidans	2 (4.17)	0 (0)
Co-infection		
Pseudomonas aeruginosa + *cytomegalovirus*	0 (0)	2 (4.17)

Footnote: Data are presented as absolute numbers (%).

real circulation. Another beneficial effect of this intervention is that operative time is significantly shorter.

Conclusions

CABG with non-extracorporeal circulation offers more beneficial outcomes compared with the procedure utilizing extracorporeal circulation.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Roach EC, Bugan B. The influence of angiotensin converting enzyme-2 gene polymorphisms: what does it predict in patients with diabetes mellitus and coronary heart disease? Eur Rev Med Pharmacol Sci 2014; 18: 1685.
2) Chaoxin J, Daili S, Yanxin H, Ruwei G, Chenlong W, Yaobin T. The influence of angiotensin-converting enzyme 2 gene polymorphisms on type 2 diabetes mellitus and coronary heart disease. Eur Rev Med Pharmacol Sci 2013; 17: 2654-2659.
3) Petersen JW, Pepine CJ. Microvascular coronary dysfunction and ischemic heart disease: Where are we in 2014? Trends Cardiovasc Med 2015; 25: 98-103.
4) Bairakova Iu V, Kazachek Ia V, Gruzdeva OV, Sergeeva T, Grigor'ev AM, Ivanov SV. [The dynamics of C-reactive protein in the process of coronary artery bypass grafting in patients with ischemic heart disease]. Klin Lab Diagn 2013; 3-6. in Russian.
5) Gilpin VL. Review of an article: Surgery for small abdominal aortic aneurysms that do not cause symptoms by Filardo G, Powell JT, Martinez MA, and Ballard DJ (Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No. CDOO1835. DOI:10.1002/14651858.CDOO1835.pub3). J Vasc Nurs 2012; 30: 134.
6) Stulak JM, Dearani JA, Burkhart HM, Ammash NM, Phillips SD, Schaff HV. Coronary artery disease in adult congenital heart disease: outcome after coronary artery bypass grafting. Ann Thorac Surg 2012; 93: 116-122; discussion 122-113.
7) Bicer M, Senturk T, Yanar M, Tutuncu A, Oral AY, Ulukaya E, Serdar Z, Signak IS. Effects of off-pump versus on-pump coronary artery bypass grafting: apoptosis, inflammation, and oxidative stress. Heart Surg Forum 2014; 17: E271-276.
8) Cetin E, Ozyuksel A, Akay F. Staged off-pump coronary artery bypass grafting and radical nephrectomy in a patient with multivessel coronary artery disease and a renal tumour. BMJ Case Rep 2014; 2014: pii: bcr2013202481.
9) Takagi H, Umemoto T. Worse long-term survival after off-pump than on-pump coronary artery bypass grafting. J Thorac Cardiovasc Surg 2014; 148: 1820-1829.
10) Bakaeen FG, Chu D, Kelly RF, Holman WL, Jessen ME, Ward HB. Perioperative outcomes after on- and off-pump coronary artery bypass grafting. Tex Heart Inst J 2014; 41: 144-151.
11) Kazmierczak E, Grajek S, Kowal J, Chmara E, Grygier M, Pyda M, Bogdanski P, Cieslewicz A, Jablecka A. Prognostic usefulness of IL-6 and VEGF for the occurrence of changes in coronary arteries of pa-

tients with stable angina and implanted stents. Eur Rev Med Pharmacol Sci 2014; 18: 2169-2175.

12) Stathas T, Athanassiou SD, Drakouli S, Giannopoulou E, Mastronikolis NS, Naxakis S, Aletras AJ. MIF attenuates the suppressive effect of dexamethasone on IL-6 production by nasal polyp. Eur Rev Med Pharmacol Sci 2013; 17: 1455-1466.

13) Bielekova B, Komori M, Xu Q, Reich DS, Wu T. Cerebrospinal fluid IL-12p40, CXCL13 and IL-8 as a combinatorial biomarker of active intrathecal inflammation. PLoS One 2012; 7: e48370.

14) Carpagnano GE, Palladino GP, Lacedonia D, Koutelou A, Orlando S, Foschino-Barbaro MP. Neutrophilic airways inflammation in lung cancer: the role of exhaled LTB-4 and IL-8. BMC Cancer 2011; 11: 226.

15) Michel O, Dinh PH, Doyen V, Corazza F. Anti-TNF inhibits the airways neutrophilic inflammation induced by inhaled endotoxin in human. BMC Pharmacol Toxicol 2014; 15: 60.

16) Simao AP, Almeida TM, Mendonca VA, Santos SA, Gomes WF, Coimbra CC, Lacerda AC. Soluble TNF receptors are produced at sites of inflammation and are inversely associated with self-reported symptoms (WOMAC) in knee osteoarthritis. Rheumatol Int 2014; 34: 1759-1763.

17) Jia Z, Babu PV, Si H, Nallasamy P, Zhu H, Zhen W, Misra HP, Li Y, Liu D. Genistein inhibits TNF-alpha-induced endothelial inflammation through the protein kinase pathway A and improves vascular inflammation in C57BL/6 mice. Int J Cardiol 2013; 168: 2637-2645.

18) Aregger F, Pilop C, Uehlinger DE, Brunisholz R, Carrel TP, Frey FJ, Frey BM. Urinary proteomics before and after extracorporeal circulation in patients with and without acute kidney injury. J Thorac Cardiovasc Surg 2010; 139: 692-700.

19) Mocini D, Muso P, Guendouz E, De Marco L, Mele L, Cini R, Sordini P, Alois A, Costantino A, Arima S, Gentili C, Santini M. Endogenous erythropoietin and a single bolus of 40,000 IU of epoetin alpha do not protect the heart from ischaemia-reperfusion injury during extracorporeal circulation for cardiac surgery. Perfusion 2008; 23: 187-192.

20) Karam MC, Merckbawi R, El-Kouba JE, Bazzi SI, Bodman-Smith KB. In Leishmania major-induced inflammation, interleukin-13 reduces hyperalgesia, down-regulates IL-1beta and up-regulates IL-6 in an IL-4 independent mechanism. Exp Parasitol 2013; 134: 200-205.

21) Bernard NJ. Inflammation: a TLR5-TNF positive feedback loop in rheumatoid arthritis. Nat Rev Rheumatol 2014; 10: 637.

22) Rajendran K, Devarajan N, Ganesan M, Ragunathan M. Obesity, Inflammation and Acute Myocardial Infarction - Expression of leptin, IL-6 and high sensitivity-CRP in Chennai based population. Thromb J 2012; 10: 13.

23) Kanoh S, Tanabe T, Rubin BK. Dapsone inhibits IL-8 secretion from human bronchial epithelial cells stimulated with lipopolysaccharide and resolves airway inflammation in the ferret. Chest 2011; 140: 980-990.

24) Yoshitaka T, Ishida S, Mukai T, Kittaka M, Reichenberger EJ, Ueki Y. Etanercept administration to neonatal SH3BP2 knock-in cherubism mice prevents TNF-alpha-induced inflammation and bone loss. J Bone Miner Res 2014; 29: 1170-1182.

25) Sedger LM, McDermott MF. TNF and TNF-receptors: From mediators of cell death and inflammation to therapeutic giants--past, present and future. Cytokine Growth Factor Rev 2014; 25: 453-472.