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➡️ **Research Article**

Elevated Levels of Interleukin-21 in Acute Kidney Injury After Cardiopulmonary Bypass Surgery

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Abstract

Background: It is well-established that complications following cardiopulmonary bypass (CPB) such as acute kidney injury (AKI) lead to worse outcomes and higher mortality. Considering the importance of the post-CPB inflammatory cytokine cascade, we first assessed the post-operative interleukin (IL)-21 serum level and its association with AKI development after CPB.

Methods: In this experimental before-after study, 40 patients with confirmed CPB-AKI in the Jorjani Heart Center, Bandar Abbas (from January 2017 to September 2018) were compared with 50 non-AKI patients. AKI was defined according to the Acute Kidney Injury Network. The IL-21 serum level was measured using an enzyme-linked immunosorbent assay before and 12 hours after surgery. The association between IL-21 and other variables was evaluated by correlation analyses.

Results: The IL-21 serum level was significantly higher post-operation compared to its level before surgery in AKI (21.4 ± 6.3 and 15.7 ± 5.5, $P < 0.001$) and non-AKI (19.1 ± 6.4 and 13.7 ± 6.3, $P < 0.001$) patients, but no significant differences were observed between AKI and non-AKI patients. Age, body mass index, and creatinine were not significantly correlated with the IL-21 serum level 12 hours post operations in AKI and non-AKI subjects.

Conclusion: Serum IL-21 concentrations were significantly increased in CPB patients after operation, which may contribute to the post-CPB inflammatory response syndrome. Our data did not confirm any association between increased IL-21 levels and CPB-AKI risk.

Keywords: Cardiopulmonary bypass, Acute kidney injury, Interleukin-21

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Background

Acute kidney injury following cardiopulmonary bypass (AKI-CPB) is associated with more morbidity and mortality and the financial burden of medical care expenses (1). Previous studies showed that factors, including contact activation from the exposure of blood to the CPB circuit, surgical trauma, ischemia-reperfusion injury, and release of endotoxin during (CPB) surgery, throw immunologic homeostasis into disarray and induce a systemic inflammatory response (2). This postoperative inflammatory response has a complex nature. It involves complement and leukocyte activation and the production of various mediators and cytokines, including platelet-activating factor, nitric oxide, oxygen-free radicals, and arachidonic acid metabolites, which are all implicated in the development of AKI-CPB (3). Several studies reported the association of the elevated plasma concentrations of inflammatory cytokines such as tumor necrosis factor, interleukin (IL)-1, and IL-6 with a subsequent AKI-CPB diagnosis (4, 5). Recently, the role of T-helper (Th) 17-related cytokines such as IL-17 and IL-23 in AKI has been demonstrated by some studies (6-8). Paust et al revealed the presence of Th17, producing IL-17, in the nephritic mouse kidney. Their study in experimental glomerulonephritis demonstrated that the IL-23/IL-17 pathway plays a significant role in renal tissue injury (6). Woltman et al studied the influence of IL-17 on tubular cells. They found that the IL-17 and CD40-ligand synergistically enhance cytokine and chemokines C-X-C motif ligand 8 (CXCL8)/IL-8 and CCL2/monocyte chemoattractant protein-1 (MCP-1) production by renal epithelial cells (9), which have significant roles in the recruitment of inflammatory cells into the injured kidney (10).

IL-21, one of the six members of the common γ-chain cytokine family, is a novel cytokine of the Th17 lineage. It has significant homology with IL-2 and IL-4, binds to the IL-21 receptor, and activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway (11, 12). In addition, this novel cytokine exhibits a wide range of effects on different lineages, including CD4, CD8 T, and B lymphocytes, regulatory T cells, dendritic cells, natural killers, and some nonimmune cells (13-15). Several recent studies have confirmed the profound role of IL-21 in the initiation and development of several autoimmune diseases and inflammatory

maladies, including psoriasis, inflammatory bowel disease, celiac disease, rheumatoid arthritis, and type I diabetes (16-21).

Objective
However, to our knowledge, there is no published study relating to the IL-21 and AKI-CPB. Therefore, this study was performed to determine the role of IL-21 in AKI development after heart surgery.

Materials and Methods
Population
Overall, 90 patients undergoing CPB graft surgery in Shahid Mohammadi Hospital, Bandar Abbas, Iran (from January 2017 to September 2018) were enrolled in this experimental before-after study. After surgery, 40 patients developed AKI. Patients were classified according to the AKI Network (AKIN) definition (22); an increase of 0.3 mg/dL in the serum creatinine level up to 48 hours post operation is defined as AKI. This group was compared to non-AKI subjects (n = 50). Patients were excluded if they were diagnosed with autoimmune and infectious diseases, any kind of liver malfunctions and kidney disorders or transplants, hemodialysis, inflammatory disease, and pre-existing AKI. Addicted patients (except for cigarettes), patients undergoing coronary angiography 72 hours before sample collection, and patients medicated with immunosuppressive or nephrotoxic drugs were also excluded from the study. All included subjects signed written informed consent forms, and systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥90 mm Hg was defined as hypertension (23). Body weight in kilograms divided by height in meters squared was defined as the body mass index (BMI = kg/m^2). Subjects who smoked at least 2 cigarettes a day at the time of admission were defined as smokers.

Blood Samples and Data Collection
Before surgery and 12 and 48 hours after the operation, blood was obtained from patients. For the collection of serum samples, blood was coagulated at room temperature for 30 minutes and then underwent centrifugation (2600 g, 10 minutes, Sigma 2-16KL). Serum creatinine levels were evaluated before and 48 hours post-operation using the Cobas 700 analyzer (Roche Diagnostics, USA). Demographic (including age, gender, and smoking) and operation (e.g., CPB time, cross-clamp time, and ejection fraction) variables were obtained from participants' medical records.

Serum IL-21 Evaluation
The IL-21 serum level was determined using an enzyme-linked immunosorbent assay kit (Zell bio, Germany) before and 12 hours after surgery according to the provider's instructions. The IL-21 linear standard curve was developed using the standards provided by the

manufacturer. The sensitivity of the kit and the intra and inter-assay variations were 25 pg/mL and < 10%, respectively.

Statistical Analyses
Quantitative variables, including demographic and clinical data, were compared between AKI and non-AKI groups using a t test or Mann-Whitney U-test if customarily or non-normally distributed, respectively, and presented as mean ± standard deviation (SD). Categorical variables were analyzed by the chi-square test. The association between IL-21 and clinical variables analyzed using Pearson correlation and correlation coefficient (r) was reported as well. The sample size was calculated considering a precision/absolute error of 5% and a type 1 error of 5%. The SD of variables was taken from previous studies. All statistical analyses were performed with the SPSS (version 20.0, SPSS Inc., Chicago, IL, USA), and statistical significance was defined as $P < 0.05$.

Results
Clinical Characteristics and IL-21 Concentration in Study Participants
A total of 90 (40 AKI and 50 non-AKI) patients were included in this study. The severity of AKI was classified based on the AKIN criteria, and 12 (30%), 18 (45%), and 10 (25%) patients developed stages 1, 2, and 3, respectively. Clinical and operative variables are presented in Table 1. The mean age of patients in AKI and non-AKI groups was 60.1 ± 6.4 and 59.4 ± 5.1, respectively ($P = 0.5$). Eighteen men and 22 women developed AKI, and 25 men and 25 women were diagnosed as non-AKI cases. Other clinical and demographic variables were not significantly different between AKI and non-AKI subjects ($P > 0.05$). The IL-21 serum level was compared in CPB patients before and after the operation. A significant increase of IL-21 was observed 12 hours after operation compared to the amounts of this cytokine before surgery in both AKI (21.4 ± 6.3 and 15.7 ± 5.5, $P < 0.001$) and non-AKI (19.1 ± 6.4 and 13.7 ± 6.3, $P < 0.001$) participants. However, no significant difference was found between AKI and non-AKI subjects before or 12 hours after the operation (Table 1).

Association of IL-21 and Other Variables
The correlation between IL-21 and other variables, including age, BMI, and serum creatinine levels before and 48 hours after the operation was assessed, and the results (Table 2) demonstrated no significant association between IL-21 and selected variables.

Discussion
This study evaluated the post-CPB IL-21 levels and their association with AKI development. Our findings showed that IL-21 levels were significantly increased after CPB. However, there was no association between IL-21 levels

Table 1. Demography, Clinical, and Operation Variables Compared Between AKI and Non-AKI Subjects

Variables	AKI (n = 40) Mean ± SD	Non-AKI (N = 50) Mean ± SD	P Value
Age (y)	60.1 ± 6.4	59.4 ± 5.1	0.6
Gender[a]			
Male	45	50	0.6
Female	55	50	
Diabetes (%)	54.4%	51.2%	0.7
Hypertension (%)	50.3%	52.8%	0.5
BMI (kg/m²)	25.1 ± 4.1	25.3 ± 3.4	0.8
Base line plasma creatinine (mg/dL)	1 ± 0.3	1.03 ± 0.2	0.6
Urine output within 24 hours after surgery (mL/kg/h)	1.9 ± 0.5	1.8 ± 0.7	0.4
BUN before surgery (mg/dL)	11.7 ± 9.4	10.1 ± 2.5	0.2
BUN 24 hours after surgery (mg/dL)	27.1 ± 6.3	25.5 ± 5.1	0.2
Systolic blood pressure (mm Hg)	135.2 ± 26.7	129.4 ± 27.9	0.3
Diastolic blood pressure (mm Hg)	75.5 ± 21.3	72.3 ± 11.4	0.4
Cross-clamp time	83.4 ± 32.5	74.7 ± 31.1	0.2
Bypass time	132.2 ± 35.8	128.4 ± 37.2	0.6
IL-21 pg/mL (before operation)	15.7 ± 5.5*	13.7 ± 6.3#	0.1
IL-21 pg/mL (after operation)	21.4 ± 6.3*	19.1 ± 6.4#	0.09

Note. SD: Standard deviation; BMI: Body mass index; BUN: Blood urea nitrogen; IL: *Interleukin*.
[a] Data are expressed as percent.
* $P < 0.001$, # $P < 0.001$.

Table 2. Associations of IL-21 Serum Levels 12 Hours Post Operation and Clinical Variables Investigated Using Pearson Correlation Analysis

Variable	Correlation Coefficient (R)	P Value
AKI Patients		
Age	-0.3	0.4
BMI	0.2	0.6
Base line plasma creatinine	-0.2	0.5
Creatinine 48 hours post operation	0.4	0.2
Non-AKI Patients		
Age	0.3	0.5
BMI	0.09	0.3
Base line plasma creatinine	-0.3	0.2
Creatinine 48 hours post operation	0.4	0.2

Note. BMI: Body mass index; AKI: Acute kidney injury.

and the incidence of AKI- CPB. Our results about the higher post-CPB levels of IL-21 are consistent with those of previous studies, confirming the elevated concentration of IL-21 in many inflammatory diseases such as asthma (24), airway allergic inflammation (25), inflammatory bowel disease (26), experimental autoimmune encephalitis, and (27) psoriasis (28). Our findings are also in line with those of studies that reported that mice deficient in IL-21 or IL-21R had reduced inflammatory responses following experimental colitis (29) and parasitic infections (30). Moreover, our results are consistent with

the findings of previous studies, demonstrating a shift in the cytokine balance toward a predominant pro-inflammatory type after CPB (31). Although the exact mechanism of how the increased levels of IL-21A may affect the postoperative inflammatory response needs further investigations, there is some explanatory evidence in this regard. First, IL-21 is not only produced by Th17 cells but also induces IL-17 production via STAT3-dependent mechanisms (11). The results of the study by Yang et al on human CD4 T cells represented that IL-21 accompanying transforming growth factor-beta has a role in the differentiation of naive T cells into Th17 cells (13), which are involved in the pathogenesis of post-CPB systemic inflammatory response syndrome (32). IL-21 also up-regulates the IL-23R expression necessary for the development of Th17 cells (14). Second, IL-21 decreases CD4 T cells' response to the suppressive effects of Treg cells, which can disturb immunologic homeostasis (33). Third, IL-21 plays a critical role in the differentiation of human B cells and immunoglobulin (Ig) production (34). It is noteworthy that the correlation of some antibodies (e.g., heart-reactive antibodies) with postcardiotomy syndrome in patients undergoing a procedure bypass has been reported previously (35).

Contrary to our assumptions, our data did not approve any association between increased IL-21 and CPB-AKI risk. This finding contradicts those of earlier studies that confirmed the effects of Th17-related cytokines on the development of renal injuries in kidney ischemia-reperfusion injury, glomerulonephritis, and lupus nephritis (6-8). Our results did not support those of Herber et al, indicating that MRL-Fas*lpr* mice treated with anti-IL-21R/Fc did not have thickening in glomerular basement membranes and revealed reduced levels of glomerular IgG deposits in the kidney (36). Our study had some limitations, including a relatively small sample size, thus caution is still appropriate in generalizing our result. The continuation of the study should allow us to give a more precise picture of the IL-21 effect on the CPB-AKI incidence. Further large prospective studies are recommended in this respect. Generally, it seems that IL-21 as a competent inflammatory mediator, not only exerts its effects through its own signaling but also via modulating other members of the IL-17 family, may contribute to systemic inflammatory responses after CPB. We also demonstrated that IL-21 could not be a biomarker in predicting renal outcomes in patients after CPB.

Authors' Contribution
NN developed the concept, and prepared the manuscript, MM performed experimentation, MR analyzed data, prepared figures and tables, wrote the method and result sections and carefully read the manuscript. HM and MKH prepared the samples. All authors

read and approved the final article.

Conflict of Interests

The authors declare that they have no competing interests.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The Ethics Committee of Hormozgan University of Medical Sciences confirmed the study (Reference number: HUMS. REC.1396.124).

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References

1. Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, Thottakkara P, Efron PA, Moore FA, et al. Cost and mortality associated with postoperative acute kidney injury. Ann Surg. 2015;261(6):1207-14. doi: 10.1097/sla.0000000000000732.

2. Seabra VF, Alobaidi S, Balk EM, Poon AH, Jaber BL. Off-pump coronary artery bypass surgery and acute kidney injury: a meta-analysis of randomized controlled trials. Clin J Am Soc Nephrol. 2010;5(10):1734-44. doi: 10.2215/cjn.02800310.

3. Levy JH, Tanaka KA. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg. 2003;75(2):S715-S20. doi: 10.1016/s0003-4975(02)04701-x.

4. Zhang WR, Garg AX, Coca SG, Devereaux PJ, Eikelboom J, Kavsak P, et al. Plasma IL-6 and IL-10 concentrations predict AKI and long-term mortality in adults after cardiac surgery. J Am Soc Nephrol. 2015;26(12):3123-32. doi: 10.1681/asn.2014080764.

5. Drabe N, Zünd G, Grünenfelder J, Sprenger M, Hoerstrup SP, Bestmann L, et al. Genetic predisposition in patients undergoing cardiopulmonary bypass surgery is associated with an increase of inflammatory cytokines. Eur J Cardiothorac Surg. 2001;20(3):609-13. doi: 10.1016/s1010-7940(01)00842-9.

6. Paust HJ, Turner JE, Steinmetz OM, Peters A, Heymann F, Hölscher C, et al. The IL-23/Th17 axis contributes to renal injury in experimental glomerulonephritis. J Am Soc Nephrol. 2009;20(5):969-79. doi: 10.1681/asn.2008050556.

7. Madhur MS, Lob HE, McCann LA, Iwakura Y, Blinder Y, Guzik TJ, et al. Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. Hypertension. 2010;55(2):500-7. doi: 10.1161/hypertensionaha.109.145094.

8. Pisitkun P, Ha HL, Wang H, Claudio E, Tivy CC, Zhou H, et al. Interleukin-17 cytokines are critical in development of fatal lupus glomerulonephritis. Immunity. 2012;37(6):1104-15. doi: 10.1016/j.immuni.2012.08.014.

9. Woltman AM, De Haij S, Boonstra JG, Gobin SJP, Daha MR, van Kooten C. Interleukin-17 and CD40-ligand synergistically enhance cytokine and chemokine production by renal epithelial cells. J Am Soc Nephrol. 2000;11(11):2044-55. doi: 10.1681/asn.v11112044.

10. Furuichi K, Wada T, Kaneko S, Murphy PM. Roles of chemokines in renal ischemia/reperfusion injury. Front Biosci. 2008;13:4021-8. doi: 10.2741/2990.

11. Wei L, Laurence A, Elias KM, O'Shea JJ. IL-21 is produced by Th17 cells and drives IL-17 production in a STAT3-dependent manner. J Biol Chem. 2007;282(48):34605-10. doi: 10.1074/jbc.M705100200.

12. Ozaki K, Kikly K, Michalovich D, Young PR, Leonard WJ. Cloning of a type I cytokine receptor most related to the IL-2 receptor beta chain. Proc Natl Acad Sci U S A. 2000;97(21):11439-44. doi: 10.1073/pnas.200360997.

13. Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, et al. IL-21 and TGF-beta are required for differentiation of human TH17 cells. Nature. 2008;454(7202):350-2. doi: 10.1038/nature07021.

14. Zhou L, Ivanov, II, Spolski R, Min R, Shenderov K, Egawa T, et al. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. Nat Immunol. 2007;8(9):967-74. doi: 10.1038/ni1488.

15. Nurieva R, Yang XO, Martinez G, Zhang Y, Panopoulos AD, Ma L, et al. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. Nature. 2007;448(7152):480-3. doi: 10.1038/nature05969.

16. De Nitto D, Sarra M, Pallone F, Monteleone G. Interleukin-21 triggers effector cell responses in the gut. World J Gastroenterol. 2010;16(29):3638-41. doi: 10.3748/wjg.v16.i29.3638.

17. van Heel DA, Franke L, Hunt KA, Gwilliam R, Zhernakova A, Inouye M, et al. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. Nat Genet. 2007;39(7):827-9. doi: 10.1038/ng2058.

18. Asano K, Ikegami H, Fujisawa T, Nishino M, Nojima K, Kawabata Y, et al. Molecular scanning of interleukin-21 gene and genetic susceptibility to type 1 diabetes. Hum Immunol. 2007;68(5):384-91. doi: 10.1016/j.humimm.2007.01.009.

19. Teixeira VH, Pierlot C, Migliorini P, Balsa A, Westhovens R, Barrera P, et al. Testing for the association of the KIAA1109/Tenr/IL2/IL21 gene region with rheumatoid arthritis in a European family-based study. Arthritis Res Ther. 2009;11(2):R45. doi: 10.1186/ar2654.

20. Costanzo A, Chimenti MS, Botti E, Caruso R, Sarra M, Monteleone G. IL-21 in the pathogenesis and treatment of skin diseases. J Dermatol Sci. 2010;60(2):61-6. doi: 10.1016/j.jdermsci.2010.08.016.

21. Botti E, Spallone G, Caruso R, Monteleone G, Chimenti S, Costanzo A. Psoriasis, from pathogenesis to therapeutic strategies: IL-21 as a novel potential therapeutic target. Curr Pharm Biotechnol. 2012;13(10):1861-7. doi: 10.2174/138920112802273281.

22. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31. doi: 10.1186/cc5713.

23. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42(6):1206-52. doi: 10.1161/01.HYP.0000107251.49515.c2.

24. Halwani R, Sultana A, Vazquez-Tello A, Jamhawi A, Al-Masri AA, Al-Muhsen S. Th-17 regulatory cytokines IL-21, IL-23, and IL-6 enhance neutrophil production of IL-17 cytokines during asthma. J Asthma. 2017;54(9):893-904. doi: 10.1080/02770903.2017.1283696.

25. Tortola L, Pawelski H, Sonar SS, Ampenberger F, Kurrer M, Kopf M. IL-21 promotes allergic airway inflammation by driving apoptosis of FoxP3+ regulatory T cells. J Allergy Clin Immunol. 2019;143(6):2178-89.e5. doi: 10.1016/j.jaci.2018.11.047.

26. Liu Z, Yang L, Cui Y, Wang X, Guo C, Huang Z, et al. Il-21 enhances NK cell activation and cytolytic activity and induces Th17 cell differentiation in inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(8):1133-44. doi: 10.1002/ibd.20923.

27. Lee Y, Mitsdoerffer M, Xiao S, Gu G, Sobel RA, Kuchroo VK. IL-21R signaling is critical for induction of spontaneous experimental autoimmune encephalomyelitis. J Clin Invest. 2015;125(11):4011-20. doi: 10.1172/jci75933.

28. Wang Y, Wang LL, Yang HY, Wang FF, Zhang XX, Bai YP. Interleukin-21 is associated with the severity of psoriasis vulgaris through promoting CD4+ T cells to differentiate into Th17 cells. Am J Transl Res. 2016;8(7):3188-96.

29. Fina D, Sarra M, Fantini MC, Rizzo A, Caruso R, Caprioli F, et al. Regulation of gut inflammation and th17 cell response by interleukin-21. Gastroenterology. 2008;134(4):1038-48.e2. doi: 10.1053/j.gastro.2008.01.041.

30. Solaymani-Mohammadi S, Eckmann L, Singer SM. Interleukin (IL)-21 in inflammation and immunity during parasitic diseases. Front Cell Infect Microbiol. 2019;9:401. doi: 10.3389/fcimb.2019.00401.

31. Gasz B, Lenard L, Racz B, Benko L, Borsiczky B, Cserepes B, et al. Effect of cardiopulmonary bypass on cytokine network and myocardial cytokine production. Clin Cardiol. 2006;29(7):311-5. doi: 10.1002/clc.4960290708.

32. He Y, Chen X, Guo X, Yin H, Ma N, Tang M, et al. Th17/Treg ratio in serum predicts onset of postoperative atrial fibrillation after off-pump coronary artery bypass graft surgery. Heart Lung Circ. 2018;27(12):1467-75. doi: 10.1016/j.hlc.2017.08.021.

33. Peluso I, Fantini MC, Fina D, Caruso R, Boirivant M, MacDonald TT, et al. IL-21 counteracts the regulatory T cell-mediated suppression of human CD4+ T lymphocytes. J Immunol. 2007;178(2):732-9. doi: 10.4049/jimmunol.178.2.732.

34. Spolski R, Leonard WJ. Interleukin-21: basic biology and implications for cancer and autoimmunity. Annu Rev Immunol. 2008;26:57-79. doi: 10.1146/annurev.immunol.26.021607.090316.

35. McCabe JC, Ebert PA, Engle MA, Zabriskie JB. Circulating heart-reactive antibodies in the postpericardiotomy syndrome. J Surg Res. 1973;14(2):158-64. doi: 10.1016/0022-4804(73)90025-5.

36. Herber D, Brown TP, Liang S, Young DA, Collins M, Dunussi-Joannopoulos K. IL-21 has a pathogenic role in a lupus-prone mouse model and its blockade with IL-21R.Fc reduces disease progression. J Immunol. 2007;178(6):3822-30. doi: 10.4049/jimmunol.178.6.3822.