European Review for Medical and Pharmacological Sciences 2017; 21: 4362-4368

# Inflammatory factor in donor liver and its effect on recipient myocardial injury after liver transplantation

J.-B. CHEN, G.-Y. CHEN, S.-D. WEI, J.-J. SUN, G.-B. LIU, Z.-T. XIE, G.-F. TANG

Liver Transplantation Ward, Department of Hepatic and Biliary Pancreatic Surgery, Henan Provincial People's Hospital, Zhengzhou, Henan, P.R. China

**Abstract. – OBJECTIVE: To study the inflammatory factors in donor livers and its effect on recipient myocardial injury after liver transplantation recipients.**

**PATIENTS AND METHODS: Eighteen patients who underwent orthotopic liver transplantations between January 2014 and December 2015 in our hospital were selected. A portion of the hepatic venous blood of donor's livers was preserved in heparinized tubes after partial resection. The concentrations of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), cardiac troponin I (cTnI), creatine kinase isoenzyme (CK-MB), and the activity of lactate dehydrogenase (LDH) in serum were measured. The concentrations of TNF-α, IL-6, cTnI, and CK-MB, and the activity of LDH in serum from the central venous blood of recipients were measured at several time points.**

**RESULTS: Persistent myocardial injuries were found in five patients, six experienced a transient increase of cardiac markers after surgery and returned to normal levels 24 h after surgery, and the others were normal. The comparison of the levels of inflammatory factors in serum between the five donors and recipients at different stages showed that the levels of myocardial markers of the donor livers which were supplied to the five cardiac injured patients were all significantly higher than those of other donor's livers, while the levels of serum inflammatory factors in recipients showed no changes during the T0-T2 stage but increased significantly during T3-T5 ($p < 0.05$). The cardiac function after surgery was significantly different from that before surgery and that of the recipients without myocardial injury ($p < 0.05$).**

**CONCLUSIONS: Blood pressure changes before surgery may affect the levels of inflammatory factors in donor's liver and cause postoperative myocardial injury in recipients. Proper hypotensive therapy for donors before partial liver resection can prevent postoperative myocardial injury in recipients.**

Key Words:
Liver transplantation, Inflammatory factor, Myocardial injury.

## Introduction

Liver transplantation is an effective treatment method for patients with end-stage hepatic diseases, hepatic failure, and hepatic failure related complications. It can also be applied for hepatic failure caused by several factors, such as inherited metabolic diseases which affect the liver (i.e. familial hypercholesterolemia) or malignant carcinoma (i.e., hepatic cell carcinoma and hepatoblastoma). With the development of surgical methods and the expanded scope of indications, the survival rate of patients with orthotopic liver transplantation has markedly increased during the past 3 years[1]. When the livers for transplantation are from organ donors, besides the basic diseases they may have, the levels of inflammatory factors in their hepatic tissues are generally relatively high. These inflammatory factors can be released into the peripheral blood of recipients after transplantation with the establishment of hepatic vein circulation and portal vein circulation[2,3]. This is also the reason why patients prone to experience explosive inflammation and myocardial injury after liver transplantation[4]. Myocardial inhibition is usually quite obvious, especially in the early stage of reperfusion of new liver in patients with liver transplantation. The clinical manifestations include significant decreases in mean arterial pressure, cardiac output, cardiac index, and stroke volume, but the underlying mechanisms are still unclear.


*Corresponding Author:* Jianbin Chen, MD; e-mail: chenjianbin0819@163.com

Based on previous studies, the aim of the present study was to further evaluate the effect of the levels of inflammatory factors on the determination of myocardial injury of the recipients via analyzing the clinical data from 18 liver transplantation recipients who were suffering from myocardial injury after transplantation. Also, the expression levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), cardiac troponin I (cTnI), creatine kinase isoenzyme (CK-MB), and lactate dehydrogenase (LDH) activity were analyzed.

## Patients and Methods

### Inclusion Criteria

(1) Patients with indications for liver transplantation; (2) Patients over 18 years old; (3) Patients with a cardiac functional grade of A or B according to the grading system of the American Heart Association (AHA).

### Exclusion Criteria

(1) Patients were not accompanied with hepatic encephalopathy; (2) There were no significant differences in kidney and lung function compared with healthy people.

### Measurement of Levels of Inflammatory Factors in Peripheral Blood

The blood sample of recipients was preserved in heparinized tubes at -40°C. The expression levels of TNF-α and IL-6 in serum were measured by enzyme-linked immunosorbent assay (ELISA). All reagents in this study were from Wuhan Boster Biological Technology, Ltd. (Wuhan, China). All the operation were performed according to the manufacturer's instructions. The study was approved by the Ethics Committee of Henan Provincial People's Hospital.

### Echocardiography

Left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic diameter (LVESD), and left ventricular ejection fraction (LVEF) of the recipients at several time points from T0to T5 during the follow-up were recorded by Vivid Portable Color Doppler Ultrasonoscope (GE Medical Systems Israel Ltd, Shanghai, China) (transducer frequency: 2.5 MHz).

### Serological Tests

After disinfection, 4-6 ml peripheral blood of patients was collected and centrifuged. The myocardial markers of hypersensitive C-reactive protein (CRP)[3,4], brain natriuretic peptide (pro-BNP)[3,5], CK-MB, and cTnI[3,6] were measured by an Abbott fully automated biochemistry analyzer. The levels of inflammatory factors in peripheral blood and myocardial markers in liver transplantation recipients were recorded at multiple time points including before skin incision (T0), 1 min after hepato-reperfusion (T1), 2 h after hepato-reperfusion (T2), at the end of surgery (T3), 4 h after surgery (T4), and 24 h after surgery (T5). The livers in this study were all obtained from organ donors. After the donor was confirmed with brain death, the liver was obtained, and 2-3 ml hepatic portal vein blood was collected and centrifuged, and the levels of inflammatory factors and myocardial markers were measured.

### Anesthesia

Combined intravenous and inhalational anesthesia was applied for liver transplantation. Patients were sent to the operating room, and the venous channel was established. Midazolam (0.05 mg/kg) and atropine (0.3 mg/kg) were injected. An arterial pressure monitoring catheter was implanted after radial artery puncture, real time invasive arterial blood pressure was measured, and the intravenous line was opened. Induction of anesthesia was performed with 1-2 mg/kg propofol, 1 μg/kg sufentanyl, and 0.15 mg/kg cisatracurium besylate. Patients were placed under mechanical ventilation after endotracheal intubation, and the end-tidal partial pressure of $CO_2$ was maintained at about 30-35 mmHg. The fraction of inhaled oxygen was 50-60%. For anesthesia maintenance, 2-4 μg/ml propofol and 0.5 μg/kg sufentanyl were used during surgery. 1-2% sevoflurane was also used with the minimal effective concentration for anesthesia, which was usually under 4.0%. Concentrated red blood cells were infused if the concentration of hemoglobin was under 80 g/L, and fresh refrigerated plasma was infused according to the blood coagulation function of the patient.

### Statistical Analysis

SPSS21.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. The $\chi^2$-test was used for qualitative data analysis, Fisher's exact test was used for the four-fold table data of the patients who did not match the criteria of $\chi^2$-test, analysis of variance (ANOVA) was used for the comparison of normally distributed data, and a *t*-test was used for comparisons between groups. $p < 0.05$ was considered to be statistically significant.

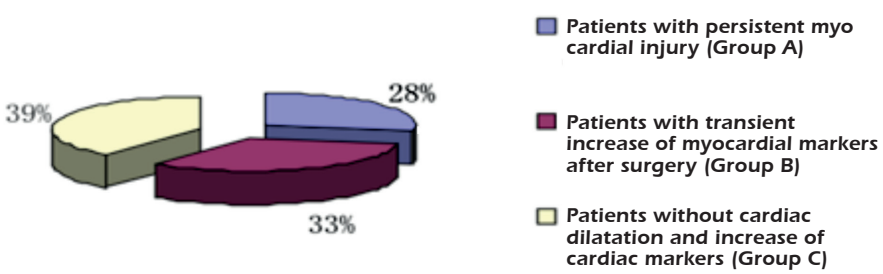


**Figure 1.** Pie chart of the distribution of recipients with myocardial injury. There were five patients suffering from persistent myocardial injury, accounting for 28% of all patients under observation in this study who underwent liver transplantation.

## Results

### Comparison of Baseline Parameters of Patients Undergoing Liver Transplantation

The operative time, anesthesia duration, volume of crystalloid solution and colloidal solution used, akaryocyte infusion, plasma infusion, bleeding volume, and urine volume of the patients undergoing liver transplantation were recorded and statistically analyzed (Table I).

### Comparison of Levels of Serum Inflammatory Factors and Myocardial Markers as Well as Indexes of Echocardiography

According to the results of echocardiography combined with the analyses of cardiac markers during follow-up, persistent myocardial injury (persistent increases of myocardial markers during the 24 h period after surgery) was found in five patients and six patients experienced a transient increase of the cardiac markers after surgery and returned to normal levels 24 h after surgery. No cardiac dilatation and increases of cardiac markers were found in the remaining seven patients. See Table II and the pie chart in Figure 1 for details. The comparison of the levels of inflammatory factors in serum of the donors and five cardiac injured recipients at multiple stages (T0-T5) showed that the levels of TNF-α, IL-6, cTnI, CK-MB, and LDH in serum from venous blood of the donor livers that were supplied to the five patients who suffered from persistent myocardial injury were significantly higher than those of other donor livers, while the levels of serum inflammatory factors of the recipients showed no changes during the T0-T2 stage but increased significantly during T3-T5 ($p < 0.05$). The increases of left ventricular end-diastolic diameter and reduction of ejection fraction were also found. The cardiac function after surgery was significantly different from that before surgery and that of the recipients with no myocardial injury, the differences were statistically significant ($p < 0.05$) (Table II).

## Discussion

After liver transplantation, all recipients will experience the pathophysiologic process of ischemia/reperfusion. During this process, large quan-

**Table I.** Comparison of baseline parameters patients undergoing liver transplantation.

| Operative time (min) | Anesthesia duration (min) | Crystalloid solution (ml) | Colloidal solution (ml) | Akaryocyte infusion (ml) | Plasma infusion (ml) | Bleeding volume (ml) | Urine volume (ml) |
|---|---|---|---|---|---|---|---|
| 642.3±151.2 | 745.3±146.2 | 1055.3±238.4 | 1562.5±430.7 | 1332.4±360.8 | 2125.7±470.6 | 1363.4±350.9 | 2342.3±545.9 |

**Table II.** The conditions of myocardial injury of patients.

| Patients with persistent myocardial injury (Group A) | Patients with transient increase of myocardial markers after surgery (Group B) | Patients without cardiac dilatation and increase of cardiac markers (Group C) |
|---|---|---|
| 5 | 6 | 7 |

**Table III.** Comparison of myocardial markers of the recipients before and after liver transplantation ($\bar{x}\pm s$).

| Index | Group | Case number | T0 | T1 | T2 | T3 | T4 | T5 | F-value | *p*-value |
|---|---|---|---|---|---|---|---|---|---|---|
| Pro-BNP | A | 5 | 10.8±0.4 | 18.5±1.4 | 18.9±2.2 | 98.7±10.9 | 138.3±22.5 | 257.8±10.2 | 9.29 | 0.01 |
| (ng/dl) | B | 6 | 9.8±0.5 | 125.1±2.3 | 119.2±3.7 | 105.3±13.8 | 152.4±14.6 | 65.4±19.2 | 4.39 | 0.02 |
| | C | 7 | 11.2±3.3 | 18.5±3.3 | 18.3±2.8 | 22.4±3.9 | 21.4±3.3 | 19.2±3.2 | 0.28 | 0.64 |
| | F-value | - | 0.48 | 8.28 | 11.33 | 9.8 | 19.7 | 28.5 | - | - |
| | *p*-value | - | 0.581 | 0.014 | 0.008 | 0.027 | 0.003 | 0.001 | - | - |
| TNF-α | A | 5 | 7.5±1.4 | 8.1±0.6 | 8.3±2.5 | 55.3±10.8 | 133.4±22.4 | 178.3±19.3 | 9.31 | 0.01 |
| (ng/ml) | B | 6 | 6.9±1.3 | 115.4±2.4 | 128.3±9.8 | 187.5±12.1 | 108.4±14.5 | 71.7±4.8 | 4.68 | 0.02 |
| | C | 7 | 7.1±2.1 | 6.8±1.9 | 7.2±2.5 | 6.9±3.7 | 8.2±1.9 | 7.3±0.6 | 0.42 | 0.55 |
| | F-value | - | 0.223 | 18.3 | 19.4 | 10.2 | 28.1 | 19.3 | - | - |
| | *p*-value | - | 0.481 | 0.006 | 0.003 | 0.021 | 0.005 | 0.003 | - | - |
| IL-6 | A | 5 | 4.7±0.3 | 5.2±0.9 | 6.0±0.4 | 28.3±9.2 | 78.4±19.4 | 104.3±21.3 | 8.38 | 0.002 |
| (ng/ml) | B | 6 | 4.9±0.4 | 98.7±10.2 | 108.4±10.2 | 99.2±9.8 | 104.5±12.7 | 66.3±7.2 | 3.28 | 0.03 |
| | C | 7 | 5.1±0.2 | 6.1±0.2 | 5.4±0.3 | 6.0±0.9 | 5.8±0.4 | 5.9±0.3 | 0.42 | 0.59 |
| | F-value | - | 0.31 | 10.2 | 9.5 | 8.3 | 19.5 | 18.8 | - | - |
| | *p*-value | - | 0.711 | 0.021 | 0.03 | 0.038 | 0.003 | 0.007 | - | - |
| cTnI | A | 5 | 0.37±0.04 | 0.42±0.03 | 0.39±0.05 | 2.48±0.26 | 3.48±0.37 | 4.28±1.39 | 9.32 | 0.03 |
| (U/L) | B | 6 | 0.24±0.02 | 2.15±0.21 | 3.14±0.4 | 3.45±0.4 | 3.07±0.3 | 1.28±0.2 | 7.28 | 0.002 |
| | C | 7 | 0.29±0.06 | 0.37±0.2 | 0.42±0.2 | 0.49±0.1 | 0.41±0.5 | 0.28±0.1 | 0.39 | 0.64 |
| | F-value | - | 0.32 | 6.81 | 9.31 | 8.42 | 7.28 | 13.4 | - | - |
| | *p*-value | - | 0.76 | 0.021 | 0.03 | 0.038 | 0.04 | 0.002 | - | - |
| CK-MB | A | 5 | 0.24±0.12 | 0.32±0.14 | 0.34±0.04 | 1.28±0.19 | 3.49±0.28 | 4.15±0.31 | 10.8 | 0.02 |
| (U/L) | B | 6 | 0.31±0.11 | 3.48±0.27 | 4.31±0.59 | 3.92±1.62 | 4.37±0.93 | 1.51±0.42 | 11.4 | 0.03 |
| | C | 7 | 0.29±0.10 | 0.38±0.1 | 0.34±0.2 | 0.49±0.3 | 0.43±0.2 | 0.51±0.3 | 0.44 | 0.57 |
| | F-value | - | 0.38 | 4.29 | 6.39 | 7.12 | 8.17 | 9.38 | - | - |
| | *p*-value | - | 0.68 | 0.04 | 0.04 | 0.04 | 0.031 | 0.002 | - | - |

tities of inflammatory factors, which mainly include TNF-α and IL-6, will be released into the recipients[5-8]. The functions of TNF-α, which is mainly secreted by inflammatory cells such as macrophages, neutrophilic granulocytes, endothelial cells, and lymphocytes, are relatively complex[9]. TNF-α performs its functions by binding its specific receptor on target cell membranes, and it is generally believed that TNF-α plays an important role in the process of inflammation[10]. IL-6 is the most sensitive inflammatory factor in the oxidative stress response of the body. It is mainly secreted by inflammatory cells such as mononuclear macrophages, activated T cells, desmocytes, and vascular endothelial cells, and plays a pivotal role in inducing the synthesis of acute phase proteins in the liver during the development of different diseases. Because the surgery for liver transplantation is generally long, patients may experience ischemia/reperfusion injury, after which large quantities of inflammatory factors will be released in the peripheral blood. Among the inflammatory factors involved in this process, TNF-α and IL-6 can cause myocardial injury after transplantation by binding to their receptors on the surface of myocardial cells, and stimulate the release of large quantities of myocardial specific proteins, such as CK-MB, Pro-BNP, and cTnI[11-15]. Moreover, Based on the results of echocardiography, which can reflect cardiac function more intuitively, it was found that reduction of the ejection fraction was common according to previous studies and the long-term clinical observation. However, the source of the numerous inflammatory factors in recipients is not clear. In this study, we found that the levels of myocardial markers as well as TNF-α and IL-6 in serum the patients who experienced transient myocardial increased significantly at 1 min of hepato-reperfusion after the recipients accepted liver transplantation. While the inflammatory factors in serum were also increased after surgery. The increase of inflammatory factors in peripheral circulation of recipients might be caused by the donor's liver. After the establishment of portal vein circulation, large quantities of inflammatory factors were re-

**Table IV.** Comparison of the echocardiography indexes.

| Index | Group | Case number | T0 | One week before surgery | t-value | *p*-value |
|---|---|---|---|---|---|---|
| LVEDD (mm) | A | 5 | 39.3±5.1 | 41.7±1.5 | 7.21 | 0.01 |
| | B | 6 | 42.5±6.6 | 46.6±3.8 | 4.32 | 0.02 |
| | C | 7 | 40.8±3.7 | 42.9±2.9 | 0.33 | 0.68 |
| | F-value | - | 0.33 | 4.9 | - | - |
| | *p*-value | - | 0.41 | 0.02 | - | - |
| LVESD (mm) | A | 5 | 34.2±2.6 | 39.8±1.6 | 8.31 | 0.008 |
| | B | 6 | 33.5±3.9 | 35.8±2.5 | 10.82 | 0.003 |
| | C | 7 | 33.5±1.4 | 34.5±1.8 | 0.87 | 0.22 |
| | F-value | - | 0.39 | 8.9 | - | - |
| | *p*-value | - | 0.62 | 0.02 | - | - |
| LVEF (%) | A | 5 | 59.2±5.8 | 61.2±2.1 | 6.31 | 0.02 |
| | B | 6 | 59.4±2.9 | 52.1±2.9 | 8.9 | 0.02 |
| | C | 7 | 58.6±2.5 | 58.3±3.8 | 0.33 | 0.65 |
| | F-value | - | 0.22 | 9.8 | - | - |
| | *p*-value | - | 0.72 | 0.01 | - | - |

**Table V.** Comparison of the levels of inflammatory factors in portal vein blood of donors corresponding with the recipients in each group.

| Group | Case number | TNF-α (ng/ml) | IL-6 (ng/ml) | Pro-BNP (ng/dl) | cTnI (U/L) | CK-MB (U/L) |
|---|---|---|---|---|---|---|
| A' | 5 | 5.3±1.7 | 4.0±0.8 | 10.8±0.4 | 0.28±0.03 | 0.39±0.05 |
| B' | 6 | 148.4±2.4 | 158.4±10.2 | 155.1±12.3 | 3.64±0.8 | 4.91±0.79 |
| C' | 7 | 5.2±1.5 | 3.4±0.2 | 11.2±3.3 | 0.29±0.02 | 0.22±0.11 |
| F-value | - | 10.2 | 11.7 | 10.8 | 8.28 | 2.19 |
| *p*-value | - | 0.022 | 0.021 | 0.023 | 0.037 | 0.048 |

Note: A' Corresponding donor of group A; B' Corresponding donor of group B; C' Corresponding donor of group C.

leased in the peripheral blood of recipients, which can further aggravate myocardial injury. However, different from the pathogenic mechanism of persistent myocardial injury, it was found that in most patients who suffered from persistent myocardial injury after surgery, the levels of inflammatory factors and myocardial markers in serum were relatively stable at the T0-T2 stage, but the inflammatory factors and myocardial markers in peripheral blood showed significant increases from the T3 stage. This possibly indicated that the inflammatory factors and myocardial markers in the body of recipients were from their own tissues during the process of ischemia/reperfusion injury, and had no correlation with the levels of inflammatory factors in the donor's liver. Furthermore, the levels of inflammatory factors and myocardial markers were not significantly increased under normal conditions. Myocardial injury of this kind can recover to a relatively normal level with the completion of surgery.

Given this, we further studied the different donors supplying livers and found that the recipients who suffered from persistent myocardial injury after transplantation all received the donors supplying livers to from the donors who had different degrees of cardiovascular diseases, such as hypertension and cardiac hypertrophy before organ donation. Furthermore, some of the donors usually had long period of antihypertensive or anticoagulants drugs treatment, and these basic diseases might cause the increased levels of inflammatory factors in donor's liver. Marfella et al16 suggested that nitric oxide (NO) might be a key factor in the negative myocardial inotropic action of TNF-α. TNF-α can induce the overexpression of nitric oxide synthase in myocardial cells, which caused large production of NO and reduction of the reaction of myoneme to $Ca^{2+}$, thus leading to negative myocardial inotropic action. It was confirmed by *ex vivo* experiments in myocardial cells that IL-10 could resist the oxidative stress

response caused by TNF-α, thus preventing myocardial injury. The balance between the two factors is therefore of great physiological significance for myocardial protection[17-19].

## Conclusions

We suggested that myocardial injury of liver transplant recipients had different mechanisms. The levels of inflammatory factors in the liver of donors might be correlated with persistent myocardial injury in the recipients. Monitoring the dynamic changes of inflammatory factors at different surgical times is important for determining the mechanism of myocardial injury and the procedures for treatment.

### Acknowledgments

This work was supported by the Grants from the Nation Natural Science Foundation of China- "The Role of GITRL in Immune Tolerance Reconstruction in Kupffer Cells of Rat Liver Transplantation" [Grant numbers 81370577].

### Conflict of interest

The authors declare no conflicts of interest.

## References

1) Lucidi C, Ginanni CS, Abraldes JG, Merli M, Tandon P, Ferri F, Parlati L, Lattanzi B, Poli E, Di Gregorio V, Farcomeni A, Riggio O. Hepatic encephalopathy expands the predictivity of model for end-stage liver disease in liver transplant setting: evidence by means of 2 independent cohorts. Liver Transpl 2016; 22: 1333-1342.
2) Soejima Y, Taguchi T, Sugimoto M, Hayashida M, Yoshizumi T, Ikegami T, Uchiyama H, Shirabe K, Maehara Y. Three-dimensional printing and biotexture modeling for preoperative simulation in living donor liver transplantation for small infants. Liver Transpl 2016; 22: 1610-1614.
3) Gastaca M, Valdivieso A, Bustamante J, Fernandez JR, Ruiz P, Ventoso A, Testillano M, Palomares I, Salvador P, Prieto M, Montejo M, Suarez MJ, de Urbina JO. Favorable longterm outcomes of liver transplant recipients treated de novo with once-daily tacrolimus: results of a single-center cohort. Liver Transpl 2016; 22: 1391-1400.
4) Bodzin AS, Lunsford KE, Markovic D, Harlander-Locke MP, Busuttil RW, Agopian VG. Predicting mortality in patients developing recurrent hepatocellular carcinoma after liver transplantation: Impact of treatment modality and recurrence characteristics. Ann Surg 2016:
5) Renteria AS, Levine JE, Ferrara JL. Development of a biomarker scoring system for use in graft-versus-host disease. Biomark Med 2016; 10: 793-795.
6) Deddens JC, Vrijsen KR, Colijn JM, Oerlemans MI, Metz CH, van der Vlist EJ, Nolte-'T HE, den Ouden K, Jansen OLS, van der Spoel TI, Koudstaal S, Arkesteijn GJ, Wauben MH, van Laake LW, Doevendans PA, Chamuleau SA, Sluijter JP. Circulating extracellular vesicles contain miRNAs and are released as early biomarkers for cardiac injury. J Cardiovasc Transl Res 2016; 9: 291-301.
7) Altun GT, Arslantas MK, Cinel I. Primary Graft Dysfunction after Lung Transplantation. Turk J Anaesthesiol Reanim 2015; 43: 418-423.
8) Guerrini GP, Berretta M, Tarantino G, Magistri P, Pecchi A, Ballarin R, Di Benedetto F. Multimodal oncological approach in patients affected by recurrent hepatocellular carcinoma after liver transplantation. Eur Rev Med Pharmacol Sci 2017; 21: 3421-3435.
9) Cocking S, Landman T, Benson M, Lord R, Jones H, Gaze D, Thijssen DH, George K. The impact of remote ischemic preconditioning on cardiac biomarker and functional response to endurance exercise. Scand J Med Sci Sports 2016.
10) Zeng RX, Li JJ, Liao PD, Zhang MZ. Relationship of non-cardiac biomarkers with periprocedural myocardial injury in patients undergoing percutaneous coronary intervention. INT J Cardiol 2016; 221: 726-733.
11) Deddens JC, Vrijsen KR, Colijn JM, Oerlemans MI, Metz CH, van der Vlist EJ, Nolte-'T HE, den Ouden K, Jansen OLS, van der Spoel TI, Koudstaal S, Arkesteijn GJ, Wauben MH, van Laake LW, Doevendans PA, Chamuleau SA, Sluijter JP. Circulating extracellular vesicles contain miRNAs and are released as early biomarkers for cardiac injury. J Cardiovasc Transl Res 2016; 9: 291-301.
12) Moriyama T, Hagihara S, Shiramomo T, Nagaoka M, Iwakawa S, Kanmura Y. Comparison of three early biomarkers for acute kidney injury after cardiac surgery under cardiopulmonary bypass. J Intensive Care 2016; 4: 41.
13) Chan WW, Waltman JK, Friedman HS, Navaratnam P. Association between cardiac, renal, and hepatic biomarkers and outcomes in patients with acute heart failure. Hosp Pract (1995) 2016; 44: 138-145.
14) Neves AL, Henriques-Coelho T, Leite-Moreira A, Areias JC. Cardiac injury biomarkers in paediatric age: Are we there yet? Heart Fail Rev 2016; 21: 771-781.
15) Kuhne M, Suter Y, Altmann D, Ammann P, Schaer B, Osswald S, Sticherling C. Cryoballoon versus radiofrequency catheter ablation of paroxysmal atrial fibrillation: Biomarkers of myocardial injury, recurrence rates, and pulmonary vein reconnection patterns. Heart Rhythm 2010; 7: 1770-1776.

16) Marfella R, Di Filippo C, Portoghese M, Ferraraccio F, Rizzo MR, Siniscalchi M, Musacchio E, D'Amico M, Rossi F, Paolisso G. Tight glycemic control reduces heart inflammation and remodeling during acute myocardial infarction in hyperglycemic patients. J Am Coll Cardiol 2009; 53: 1425-1436.

17) Weil BR, Manukyan MC, Herrmann JL, Wang Y, Abarbanell AM, Poynter JA, Meldrum DR. Mesenchymal stem cells attenuate myocardial functional depression and reduce systemic and myocardial inflammation during endotoxemia. Surgery 2010; 148: 444-452.

18) Cohen SS, Min M, Cummings EE, Chen X, Sadowska GB, Sharma S, Stonestreet BS. Effects of interleukin-6 on the expression of tight junction proteins in isolated cerebral microvessels from yearling and adult sheep. Neuroimmunomodulat 2013; 20: 264-273.

19) Yildiz K, Ince AT, Sarbay KA, Sert S, Isen HC, Tozlu M, Baysal B, Akyuz U, Kocaman O, Danalioglu A. Role of serum myeloperoxidase, CPK, CK-MB, and cTnI tests in early diagnosis of myocardial ischemia during ERCP. Turk J Gastroenterol 2014; 25: 291-297.