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ORIGINAL ARTICLE

Association of NRF-2 changes in plasma and pericardial fluid with renal injury in patients undergoing cardiac surgery

Asociación de los cambios de NRF-2 en plasma y líquido pericárdico con lesión renal en pacientes sometidos a cirugía cardiaca

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Abstract

Objective: *This study was conducted to investigate the levels of nuclear factor (erythroid derivative 2)-like 2 (NRF-2), kidney injury molecule 1 (KIM-1), and heme oxygenase-1 (HO-1) in pericardial fluid (PF) and systemic circulation of patients undergoing cardiac surgery.* **Methods:** *This study included 40 patients undergoing cardiac surgery and 40 healthy individuals. PF and venous blood samples were obtained from the patients and renal function tests, HO-1, KIM-1, NRF-2, antioxidant, and oxidative stress parameters were studied.* **Results:** *A statistically significant difference was found in the NRF-2, KIM-1, HO-1, total antioxidant status, total oxidant status, and oxidative stress index measurements in the plasma of the patient and control groups and in the PF of the patients ($p < 0.01$). Compared to the control group, NRF-2, KIM-1, and HO-1 were found to be lower in the patient's plasma and PF. In the patient group, NRF-2, KIM-1, HO-1, and KIM-1 were higher in PF compared to plasma.* **Conclusions:** *In the future, intrapericardial drug administration may improve cardiac function and prevent the adverse cardiorenal syndrome on the kidney.*

Keywords: *Kidney damage. Nuclear factor (erythroid derivative 2)-like 2. Kidney injury molecule 1. Heme oxygenase-1. Cardiopulmonary bypass. Cardiac surgery.*

Resumen

Objetivo: *Investigar los niveles del factor nuclear (derivado eritroide 2) similar 2 (NRF-2), la molécula de lesión renal 1 (KIM-1) y la hemooxigenasa 1 (HO-1) en el líquido pericárdico y en la circulación sistémica de pacientes sometidos a cirugía cardiaca.* **Métodos:** *En este estudio participaron 40 pacientes sometidos a cirugía cardiaca y 40 individuos sanos. Se obtuvieron muestras de líquido pericárdico y sangre venosa de los pacientes y se estudiaron las pruebas de función renal, HO-1, KIM-1, NRF-2 y los parámetros antioxidantes y de estrés oxidativo.* **Resultados:** *Se encontró una diferencia estadísticamente significativa en las mediciones de NRF-2, KIM-1, HO-1, estado antioxidante total (TAS), estado oxidante total (TOS) e índice de estrés oxidativo (OSI) en el plasma entre los grupos de pacientes y de sujetos control, y en el líquido pericárdico de los pacientes ($p < 0.01$). En comparación con el grupo de control, se observó que NRF-2, KIM-1 y HO-1 eran más bajos en el plasma y en el líquido pericárdico de los pacientes. En el grupo de pacientes, NRF-2, KIM-1 HO-1 y KIM-1 eran más elevados en el líquido pericárdico que en el plasma.* **Conclusiones:** *En el futuro, la administración intrapericárdica de fármacos puede mejorar la función cardiaca y prevenir el síndrome cardiorrenal adverso sobre el riñón.*

Palabras clave: *Daño renal. NRF-2. KIM-1. HO-1. Bypass cardiopulmonar. Cirugía cardiaca.*

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Introduction

Many organs, especially the heart and kidney, are affected in cardiopulmonary bypass (CPB), which allows cardiovascular surgery to be performed. Many molecules are secreted from the organs affected by this condition. Many of these secreted molecules can provide important information about the relevant organ or disease by showing biomarker properties. Recently, apart from classical kidney biomarkers such as urea, uric acid, and creatinine, such as nuclear factor (erythroid derived 2)-like 2 (NRF-2), kidney damage molecule 1 (KIM-1), and heme oxygenase-1 (HO-1) new biomarkers have been discovered.

NRF-2 is an important protein that regulates the expression of antioxidant proteins that protect against oxidative damage triggered by injury and inflammation[1]. As long as it is not exposed to reactive oxygen species, NRF-2, which is degraded, passes to the nucleus without being degraded under oxidative stress, binds to DNA and initiates the transcription of antioxidative genes[2,3]. NRF-2, which provides the stimulation of many cytoprotective proteins, is found in the kidney, as well as in the muscle, lung, heart, liver, and brain[4,5].

HO-1, an enzyme synthesized in renal tubular cells, has cell protective, anti-inflammatory, and antioxidant properties and is synthesized in response to oxidative stress[6]. HO-1, whose transcriptional regulation is dependent on NRF-2, plays a role in many diseases related to endoplasmic reticulum stress, such as cardiovascular and metabolic diseases[7,8].

In some studies, kidney injury molecule 1 (KIM-1) was found to be significantly higher in patients who developed kidney damage (KD) after cardiac surgery[9]. In damaged kidney cells, KIM-1 functions as a receptor controlling apoptotic cell phagocytosis[10]. After studies on KD, the American Food and Drug Administration and the European Medicines Agency approved KIM-1, one of the seven new biomarkers to be used for the detection of nephrotoxicity[11]. Many studies have supported that KIM-1 is a useful biomarker for the early detection and diagnosis of complications after cardiac surgery and KD caused by ischemia[12].

Although these biomarkers such as NRF-2, KIM-1, and HO-1 were investigated in human plasma, they were not investigated in pericardial fluid (PF). PF has an important place in cardiovascular research due to its anatomical proximity to cardiac tissue and rich content[13]. Changes in molecular markers in PF show strong correlations with many structural and functional parameters as well as cardiac pathophysiologies. The pericardial environment is both a potential diagnostic biomarker pool and an important location for future treatment and interventions. Due to the lack of data on the physiological composition of PF in studies conducted to date, its clinical use has been limited[14].

In our study on the change of these biomarkers, which provide valuable information in the early detection of KD, during CPB, the level of the relevant parameters in the plasma was monitored and information was obtained about the level in PF.

Methods

Ethical committee approval

The present study was approved by the local ethics committee (Approval number: 29.06.2020-20.12.26).

Patients included in the study

This study was conducted in accordance with the Helsinki Declaration, which was revised in 1989. Forty patients who underwent cardiac surgery with CPB method and 40 healthy individuals as control group were included in this study. PF and venous blood samples were obtained from the patients included in the study. Only venous blood samples were taken from the control group.

Obtaining PF

After median sternotomy was performed with standard CPB procedures in patients who underwent cardiac surgery with the CPB method, the pericardium was opened and PF aspiration was provided with a sterile syringe. The aspirated PF (5-20 mL) was then taken into sterile tubes without anticoagulant, and the sterile tube was immediately transferred into an ice-filled container. Then, the PF in a sterile tube delivered to the laboratory with an ice-filled container was centrifuged at + 4°C at 5000 rpm for 5 min, and the supernatant was taken into an RNase-free tube (ependorf tube) and stored at −80°C to be studied.

Obtaining blood plasma

In patients who underwent cardiac surgery with the CPB method, blood was drawn before, during and after CPB and put into sterile tubes with anticoagulant (heparin). The tube from which blood was drawn was

immediately transferred to an ice-filled container and transported to the laboratory. The sterile tube was then centrifuged at 5000 rpm for 5 min. After the centrifugation step, the plasma, which is the supernatant part, was taken into an RNase-free tube (ependorf tube) and stored at −80 to be studied.

Biochemistry study in plasma of patient group

Glucose, urea, albumin, alanine aminotransferase (ALT), Na, creatinine, aspartate aminotransferase (AST), direct bilirubin, gamma-glutamyl transferase (GGT), calcium (Ca), and C-reactive protein (CRP) levels were measured in the plasma of the patients included in the study before the operation (preop), after the termination of CBP and after the operation (post-operative). Siemens Atellica autoanalyzer device (USA, 2018) was used to measure these parameters.

Enzyme-linked immunosorbent assay (ELISA) study in PF and plasma

PF and plasma NRF-2 ELISA study

Human NFE2L2 (Nuclear Factor, Erythroid Derived 2, Like 2) ELISA Kit (Elabscience, USA, Catalog No: E-EL-H1564) was used for NRF-2 ELISA study in PF and Plasma. This kit used works according to the double-antibody sandwich enzyme-linked immunosorbance analysis to test the NRF-2 level in biological materials. The sensitivity (sensitivity) of the kit is 0.10 ng/mL, and the assay range (Detection Range) is 0.16-10 ng/mL.

PF and plasma HO-1 ELISA study

Human HO-1 ELISA Kit (Elabscience, USA, Cat. No: E-EL-H2172) was used for HO-1 ELISA assay in PF and plasma. This kit used works according to the double-antibody sandwich enzyme-linked immunosorbance assay to test the HO-1 level in biological materials. The sensitivity of the kit is 0.19 ng/mL, and the assay range is 0.31-20 ng/mL.

Human KIM-1 ELISA study in PF and plasma

Human KIM-1 ELISA Kit (Elabscience, USA, Catalog No: E-EL-H6029) was used for the KIM-1 ELISA study in PF and plasma. This kit used works according to the double-antibody sandwich enzyme-linked immunosorbance assay to test the level of KIM-1 in biological materials. The sensitivity of the kit is 4.69 pg/mL, and the assay range (Detection Range) is 7.81-500 pg/mL.

Measurement of antioxidant and OS parameters in PF and plasma

Total antioxidant status (TAS) measurement

Measurement of (TAS in PF and plasma was performed using Rel Assay Diagnostics total oxidant capacity measurement kit (Rel Assay Diagnostics, Lot. No: HN20106A, Turkey). Plasma TAS levels were determined using a new automated measurement method developed by Erel[15].

Total oxidant status (TOS) measurement

Rel assay diagnostics total oxidant capacity measurement kit (Rel Assay Diagnostics, Lot. No: OK20115O, Turkey) was used for the measurement of TOS in PF and plasma. Plasma TOS levels were determined using a new automated measurement method developed by Erel[16].

Oxidative stress index (OSI) measurement

OSI was calculated by dividing it as total oxidant level (TOS)/total antioxidant and expressed as arbitrary unit (AU).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) Windows version 24.0 (SPSS, Inc, Chicago, USA) package program was used for statistical analysis. The conformity of the data to the normal distribution was tested with the Shaphiro Wilk test. Mann-Whitney U test was used for comparison of numerical variables in two independent groups, one-way analysis of variance and least significant difference multiple comparison tests were used for normally distributed features, and Kruskal-Wallis test and all pairwise multiple comparison test were used for non-normally distributed features. As descriptive statistics, mean ± standard deviation for numerical variables, number, and percentage values for categorical

variables are given. P < 0.05 were considered statistically significant.

Results

Demographic data of the working group

Of the patients included in the study, 25 were male and 15 were female, with a mean age of 62.58 (years), height 160.11 (cm), weight 75.40 (kg), and body surface area (BSA) 1.83 that it is calculated as (m^2).

Biochemical results in plasma of patients

The results of biochemical examinations in the plasma of the patients included in the study before the operation (preop), after CBP and after the operation (postop) are given in table 1.

ELISA results in PF and plasma

The results of the optical density reading at 450 nm using commercial kits for the level determination of HO-1, NRF-2, and KIM-1 in PF and plasma by ELISA method and the results of OS parameters are given in table 2.

Table 2 shows the statistical analysis of different biochemical parameters in pre-operative, post-CBP, and post-operative groups. According to this analysis, glucose, urea, creatinine, albumin, ALT, AST, direct bilirubin, GGT, Na, Ca, and CRP values were statistically significant (*p < 0.05, **p < 0.001).

Glucose value which was 170.23 before CPB was 201.30 after CPB and 177 post-operative (p < 0.05). Urea value which was 37.22 before CPB was 42.07 after CPB and 47.41 post-operative (p < 0.01). Creatinine value was 0.91 before CPB, 0.98 after CPB and 1.17 post-operative (p < 0.01). Albumin value which was 41.27 before CPB decreased to 29.43 after CPB and increased to 31.22 postop (p < 0.01). While ALT value was 21.26 before CPB, it became 25.89 after CPB and 28.32 post-operative (p < 0.01). AST value was 29.12 before CPB, 49.22 after CPB and 50.30 post-operative (p < 0.01). D. bilirubin value which was 0.2 before CPB was 0.15 after CPB and 0.26 post-operative (p < 0.01). GGT value which was 27.58 before CPB decreased to 24 after CPB and increased to 29.83 post-operative (p < 0.05). Na value, which was 138.20 before CPB, became 141.78 after CPB and 141.83 post-operative (p < 0.01). Ca value which was 9.17 before CPB was 8.16 after CPB and 7.85 post-operative (p < 0.01). CRP value, which was 13.38 before CPB, was 25.4 after CPB and 132.21 post-operative (p < 0.01) (Fig. 1).

As shown in Graph 1, when HO-1, NRF-2, KIM-1, TAS, TOS, and OSI values in the plasma and PF of the patients and the plasma of the control group were compared, the highest HO-1 value was found in the plasma of the control group, while the lowest HO-1 value was found in the plasma of the patients. The highest NRF-2 value was found in the plasma of the control group, while the lowest NRF-2 value was found in the patient plasma. The highest KIM-1 value was found in the plasma of the control group, while the lowest KIM-1 value was found in the PF of the patients. The highest TAS value was found in the plasma of the control group, while the lowest TAS value was found in the PF of the patients. The highest TOS value was found in the PF of the patients, while the lowest TOS value was found in the plasma of the control group. The highest OSI value was found in the PF of the patients, while the lowest OSI value was found in the plasma of the control group.

These results were statistically significant (p < 0.001). According to these results, HO-1, NRF-2, KIM-1, and TAS values were lower in the plasma of the patients compared to the plasma of the control group, while TOS and OSI values were higher. When the PF was compared with the plasma of the patients, HO-1, NRF-2, TOS, and OSI values in the PF were higher than the plasma of the patients, while KIM-1 and TAS values were lower. HO-1, NFR-2, KIM-1, and TAS values were found to be lower in pericardium, before CPB - plasma, during CPB - plasma and after CPB-plasma compared to the control group. TOS and OSI values were found to be higher in pericardium, before CPB - plasma, during CPB - plasma and after CPB-plasma compared to the control group.

According to table 3, there is a significant positive relationship between HO-1 value and NRF-2, TOS, and OSI value. There is a significant positive relationship between NRF-2 value and KIM-1, TOS, and OSI value, and a significant negative relationship between TAS value. There is a moderately significant negative relationship between TAS value and TOS and OSI value. There is a very highly significant positive relationship between TOS value and OSI value.

As shown in figure 2, the lowest HO-1 value in patient plasma was found in Pump 1, while the highest HO-1 value was found in Pump 3. The lowest NRF-2 value was found in Pump 1, while the highest NRF-2

Table 1. Biochemical test results of the patients included in the study

Parameter	Preop CPB	After CPB	Postop	p
Plasma	Mean ± SS	Mean ± SS	Mean ± SS	
Glucose (mmoL/L)	170.23 ± 70.33	201.3 ± 47.78	177 ± 41.43	0.013*
Urea (mg/dL)	37.22 ± 15.29	42.07 ± 14.98	47.41 ± 19.5	0.004*
Creatinine (mg/dL)	0.91 ± 0.71	0.98 ± 0.42	1.17 ± 0.72	0.003*
Albumin (g/dL)	41.27 ± 4.95	29.43 ± 5.8	31.22 ± 5.21	0.001*
ALT (U/L)	21.26 ± 12.18	25.89 ± 13.88	28.32 ± 11.63	0.007*
AST (birim/L)	29.12 ± 20.11	49.22 ± 28.17	50.3 ± 24.34	0.001*
Total bilirubin (mg/dL)	0.55 ± 0.31	0.7 ± 0.42	0.59 ± 0.32	0.102
Direct bilirubin (mg/dL)	0.2 ± 0.09	0.15 ± 0.1	0.26 ± 0.14	0.001*
GGT (U/L)	27.58 ± 14.92	24 ± 13.81	29.83 ± 13.31	0.043*
Na (mEq/L)	138.2 ± 3.15	141.78 ± 3.08	141.83 ± 4.29	0.001*
K (mEq/L)	4.35 ± 0.35	4.46 ± 0.46	4.27 ± 0.47	0.203
Ca (mEq/L)	9.17 ± 0.68	8.16 ± 0.71	7.85 ± 0.59	0.001*
CRP (mg/L)	13.38 ± 7.25	25.4 ± 15.75	132.21 ± 78.59	0.001*

[a]Kruskal-Wallis Test.
*p < 0.05; **p < 0.001.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; CBP: cardiopulmonary bypass; GGT: gamma-glutamyl transferase; Na: sodium; K: potassium; Ca: calcium; CRP: C-reactive protein.

Table 2. HO-1, NRF-2, KIM-1 ELISA results, and OS parameters in PF and plasma.

Parameter	Control (Plasma)	Pericardial fluid	Preop CPB (Plasma)	After CPB (Plasma)	Postop (Plasma)	p
	Mean ± SS	Mean ± SS	Mean ± SS	Mean ± SS	Mean ± SS	
HO-1 (ng/mL)	1.35 ± 0.32	0.66 ± 0.22	0.58 ± 0.16	0.72 ± 0.28	1.12 ± 0.51	0.000
NRF-2 (ng/mL)	5.63 ± 1.26	0.85 ± 0.33	0.77 ± 0.24	4.07 ± 1.71	4.55 ± 1	0.000
KIM-1 (pg/mL)	31.54 ± 17.09	18.7 ± 9.92	26.11 ± 14.8	27.69 ± 13.81	30.66 ± 19.12	0.001
TAS (Trolox equivalent/L)	1.57 ± 0.21	1.19 ± 0.35	1.45 ± 0.17	1.34 ± 0.25	1.34 ± 0.19	0.000
TOS (μmol H_2O_2 Eqv./L)	10.79 ± 1.99	17.78 ± 2.48	14.46 ± 2.32	14.96 ± 2.52	16.55 ± 2.76	0.000
OSI (Arbitrary Unit (AU))	0.71 ± 0.19	1.69 ± 0.8	1.05 ± 0.25	1.1 ± 0.24	1.28 ± 0.34	0.000

[a]Kruskal-Wallis Test.
*p < 0.05; **p < 0.001.
HO-1: heme oxygenase-1; NRF-2: nuclear factor (erythroid derivative 2)-like 2; KIM-1: kidney injury molecule 1; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index.

value was found in Pump 3. The lowest KIM-1 value was in Pump 1, while the highest KIM-1 value was in Pump 3. The highest TAS value was in Pump 1, while the lowest TAS value was in Pump 3. The lowest TOS value was in Pump 1, while the highest TOS value was in Pump 3. The lowest OSI value was found in Pump 1, while the highest OSI value was found in Pump 3. These results were statistically significant ($p < 0.001$). According to these results, HO-1, NRF-2, KIM-1, TOS, and OSI values increased and TAS value decreased ($p < 0.001$).

There is a significant positive correlation between HO-1 value and NRF-2, TOS, and OSI value. There is a positive relationship between NRF-2 value and

Table 3. Correlation of HO-1, NRF-2, KIM-1, TAS, TOS, and OSI values in patients included in the study

Parameter	HO-1	NRF-2	KIM-1	TAS	TOS	OSI
HO-1						
r	1.000	0.543**	0.104	–0.139	0.431**	0.375**
p		0.000	0.158	0.059	0.000	0.000
NRF-2						
r	0.543**	1.000	0.172*	–0.274**	0.508**	0.511**
p	0.000		0.020	0.000	0.000	0.000
KIM-1						
r	0.104	0.172*	1.000	0.147	–0.083	–0.140
p	0.158	0.020		0.05	0.263	0.059
TAS						
r	0.139	0.274**	0.147	1.000	–0.274**	–0.740**
p	0.059	0.000	0.05		0.000	0.000
TOS						
r	–0.431**	–0.508**	–0.083	–0.274**	1.000	0.819**
p	0.000	0.000	0.263	0.000		0.000
OSI						
r	–0.375**	–0.511**	–0.140	–0.740**	0.819**	1.000
p	0.000	0.000	0.059	0.000	0.000	

*p < 0.05.
**p < 0.01.
HO-1: heme oxygenase-1; NRF-2: nuclear factor (erythroid derivative 2)-like 2; KIM-1: kidney injury molecule 1; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index.

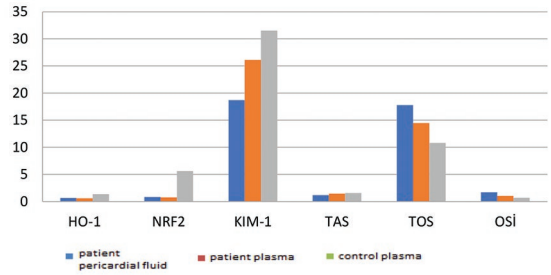

Figure 1. *Graphical display of heme oxygenase-1, nuclear factor (erythroid derivative 2)-like 2, kidney injury molecule 1, total antioxidant status, total oxidant status, and oxidative stress index values in plasma and pericardial fluid of patients and plasma of control group.*

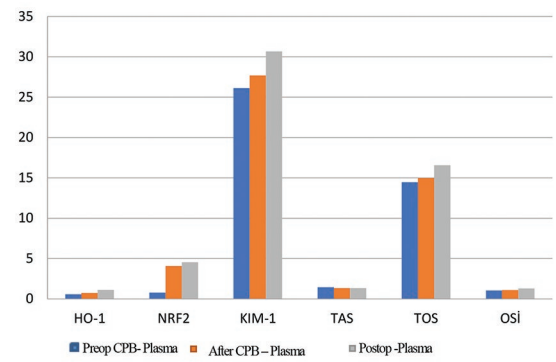

Figure 2. *Graphical representation of the changes in the heme oxygenase-1, nuclear factor (erythroid derivative 2)-like 2, kidney injury molecule 1, total antioxidant status, total oxidant status and oxidative stress index values in the plasma of the patients during before cardiopulmonary bypass (CPB) - plasma, during CPB-plasma and after CPB-plasma.*

KIM-1, TOS, and OSI values, and a negative significant relationship between TAS values. There is a moderately significant negative correlation between TAS value and TOS and OSI values. There is a highly significant positive correlation between TOS value and OSI value.

Discussion

One of the most important elements to be evaluated during CPB is the follow-up of irreversible cell and tissue damage. Before reaching this stage, the cell or tissue synthesizes biomarkers that provide information about its state. For example, in KD, NRF-2, HO-1, and KIM-1 are activated and provide information about the organ. Therefore, these parameters should be monitored during CPB and measures should be taken accordingly.

In our study, a positive correlation was found between urea, creatinine, and CRP values in the plasma of the patient group and HO-1, KIM-1, and NRF-2 values. According to this result, CPB had a negative effect on the kidneys and caused an increase in urea, creatinine, CRP, HO-1, KIM-1, and NRF-2.

In the study conducted by Magyar et al., (2019) on HO-1 and KD following cardiac surgical procedure with CPB technique, an increase in HO-1 was observed 24 h after CBP in patients who developed acute kidney injury (AKI)[17]. In another study, it was reported that AKI was associated with duration of CPB, hemolysis, inflammation, and increased HO-1 concentrations in patients after cardiac surgery[18]. In a different study, it was found that HO-1 reduces inflammation and oxidative stress, and carbon monoxide, the product of HO-1 degradation, reduces KD caused by CPB[19]. In our study, the HO-1 value, which was lower in plasma and PF of the patients compared to the control group, increased continuously during the CPB-pump ($p < 0.001$). In our study, the HO-1 value was higher in PF compared to the plasma of the same patient ($p < 0.001$). The detection of HO-1 in PF supports the view that PF is a plasma ultrafiltrate. In addition, the

detection of HO-1 in PF shows that this molecule is not only synthesized by the kidney but also by the heart tissue. A high HO-1 level during the CPB-pump period indicates that the kidney functions are affected and respond.

Some researchers believe that high KIM-1 levels can be used as an early diagnostic indicator of AKI in patients after cardiac surgery[20] and correlate with renal impairment[21]. Neyra et al., in a study of KIM-1, 23 of 106 adult patients who underwent coronary artery bypass graft (CABG) and valve surgery with CPB developed KD. In these patients, urine KIM-1/creatinine combination was found to be significantly above the optimal threshold value with post-operative KD[22]. The KIM-1 value, which was lower in plasma and PF of the patients compared to the control group, increased during the CPB process ($p < 0.001$). In our study, KIM-1 value was lower in PF compared to the plasma of the same patient ($p < 0.001$). The fact that KIM-1 was lower in PF compared to plasma indicates that this molecule is mostly synthesized in the kidneys.

In our study, the NRF-2 value, which was lower in plasma and PF of the patients compared to the control group, increased continuously during the pump ($p < 0.001$). In the same patient, NRF-2 value was higher in PF than in plasma ($p < 0.001$). While a negative significant relationship was found between NRF-2 and TAS, a positive significant relationship was found between TOS and OSI. NRF-2 value also increased in parallel with increasing OS. In this respect, NRF-2 is similar to other studies in the literature. As can be seen from the studies, promoting NRF-2-mediated protection against OS and inflammation-induced damage with different bioactive compounds may represent new therapeutic strategies. In our study, the increase of NRF-2 against the increased cellular stress and inflammatory response due to CPB was parallel to other studies in the literature.

Although NRF-2, HO-1, and KIM-1 provide important information in KD, it would not be correct to evaluate only these. Because the origin of the damage to the kidneys during CPB is multifactorial. Although CPB is the main factor in this damage, changes in hematocrit and temperature, use of vasoactive and nephrotoxic drugs, hemodynamic changes, and low cardiac output also have negative effects on the kidneys. It is interesting that some studies have reported that the incidence of KD is similar during off-pump CABG and on-pump CABG[23]. Therefore, the specific damage of CPB to the kidneys has not been clarified. However, according to studies, KD in patients with normal pre-operative renal function has a relatively low incidence compared to patients with pre-operative dysfunction. In addition, even in a patient with normal kidney function, the effect of the slightest physiological change in the heart can be felt in the kidney due to the effect of cardiorenal syndrome.

From the past to the present, different groups have tried to find treatments that can protect the kidney from damage during cardiac and non-cardiac surgery. These solutions include the use of drugs such as dopamine, furosemide, fenoldopan, atrial natriuretic factor, sodium bicarbonate, n-acetyl cysteine, enoximone, and dexmedetomidine. In addition, hypothermia and normothermia applications with high or low hematocrit during CPB are other applications to protect the kidney. However, no clear treatment or method has been found to date[24].

A 2012 study used ulinastatin, a protease inhibitor that can suppress the harmful effects of inflammatory reactions and free radicals on kidney cells during CPB[25].

As can be understood from these studies, promoting NRF-2-mediated protection against OS and inflammation-induced damage with different bioactive compounds may represent new therapeutic strategies. In our study, the high level of NRF-2 against increased cellular stress and inflammatory response due to CPB was in parallel with other studies in the literature. In particular, the level of NRF-2 increased rapidly in response to ischemia/reperfusion after cross-clamping of the aorta during CPB. This shows that NRF-2 responds rapidly to cellular reactions and is a diagnostically important parameter. It is important to follow the NRF-2 level especially in the detection of BD that may occur during CPB and to get support from the nephrology clinic to make the necessary treatment according to the level. During CPB, tissue perfusion may also be impaired due to pump pressure and ischemia/reperfusion injury may occur especially in the kidney due to insufficient blood supply. In such cases, NRF-2 may protect the kidney from damage by supporting antioxidant capacity.

Conclusions

In our study population, urea, creatinine, CRP, HO-1, NRF-2, KIM-1, TOS, and OSI increased continuously in correlation with each other during CPB and postoperatively. Compared to the plasma of the control group, HO-1, NRF-2, KIM-1, and TAS were found to be lower in the plasma of the patient group, while TOS

and OSI were found to be higher. In the patient group, HO-1, NRF-2, TOS, and OSI were higher in PF compared to plasma, while KIM-1 and TAS values were lower. It is important that all molecules in plasma were detected in PF for the first time in the study, and this supports the view that PF is a plasma ultrafiltrate. In addition, we can say that KIM-1, which is lower in Pf compared to plasma, is a molecule released mostly by the kidneys.

In CPB, KD can be prevented or reduced with therapeutic strategies that reduce the adverse effects on the kidneys. For this, it is important to develop and implement the most appropriate strategies that increase NRF-2/HO-1 and decrease KIM-1 by following the relevant parameters during CPB and postoperatively.

Two different terms can be used to describe the pathophysiologic interaction between the heart and kidney. The first one, cardiorenal, is used when cardiac dysfunction causes renal dysfunction. The second term, renocardiac, is used when renal dysfunction causes cardiac dysfunction. Future studies may examine the relationship between cardiac and renal biomarkers to determine whether the interaction between the two organs is cardiac or renal (cardiorenal or renocardiac).

The fact that PF was studied and compared with plasma for the first time, that three important parameters such as HO-1, NRF-2, and KIM-1, which are related to each other, were studied together and that the data obtained were compatible with the clinic made our study powerful.

Limitations

Our study has some limitations. This was a prospective study and included a limited number of patients. We had limitations such as not being able to analyze NRF-2, HO-1 and KIM-1 in healthy individuals because PF could not be obtained from healthy individuals, not being able to analyze the relevant parameters in urine due to budget problems and not being able to perform gene expression studies. Our main aim in this study was to investigate the prognostic value of NRF-2. Different designed studies on pathophysiologic processes are needed to elucidate the mechanisms underlying our findings.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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