Thiol/disulfide homeostasis in pericardial fluid and plasma of patients undergoing coronary artery bypass surgery

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Abstract

Background: On-pump coronary artery bypass grafting (CABG) method affect almost all biochemical reactions by disrupting the patient's redox homeostasis. Detection of systemic redox hemostasis in the patient are critical for the CABG method's success and the prognosis of the disease. In this study, thiol/disulfide parameters, which are indicators of redox homeostasis, and ischemia-modified albumin (IMA) levels in the plasma and pericardial fluid of patients who underwent coronary artery bypass surgery were investigated. **Methods:** Sixty patients who underwent an on-pump CABG operation with the Cardiopulmonary Bypass (CPB) method were included in this study. Blood samples were taken from the patients before and after the CPB. Pericardial fluid samples were taken before the CPB. Then, thiol/disulfide homeostasis, albümin, and IMA levels in the pericardial fluid, and the patients' plasma levels were compared. **Results:** Albumin and IMA levels were significantly higher in postop compared to preop ($p < 0.001$). Thiol/disulfide parameters, native thiol, total thiol, and disulfide levels were higher and statistically significant in preop than in postoperative examinations ($p < 0.001$). A negative correlation was found between pericardial fluid IMA and thiol-disulfide parameters ($p < 0.001$). **Conclusions:** Changes in thiol/disulfide homeostasis, albümin, and IMA levels at different times during the on-pump CABG may be caused by foreign non-endothelial surfaces, filters, the reperfusion process, and pharmacological effects in the extracorporeal circulation. Thiol/disulfide homeostasis, albumin, and IMA levels should be monitored during the on-pump CABG and should intervene with appropriate therapeutic strategies. In this way, secondary pathologies can be avoided by preventing cellular damage and excessive inflammatory responses.

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The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

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ABSTRACT

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Methods: Sixty patients who underwent an on-pump CABG operation with the Cardiopulmonary Bypass (CPB) method were included in this study. Blood samples were taken from the patients before and after the CPB. Pericardial fluid samples were taken before the CPB. Then, thiol/disulfide homeostasis, albümin, and IMA levels in the pericardial fluid, and the patients' plasma levels were compared.

Results: Albumin and IMA levels were significantly higher in postop compared to preop ($p < 0.001$). Thiol/disulfide parameters, native thiol, total thiol, and disulfide levels were higher and statistically significant in preop than in postoperative examinations ($p < 0.001$). A negative correlation was found between pericardial fluid IMA and thiol-disulfide parameters ($p < 0.001$).

Conclusions: Changes in thiol/disulfide homeostasis, albümin, and IMA levels at different times during the on-pump CABG may be caused by foreign non-endothelial surfaces, filters, the reperfusion process, and pharmacological effects in the extracorporeal circulation. Thiol/disulfide homeostasis, albumin, and IMA levels should be monitored during the on-pump CABG and should intervene with appropriate therapeutic strategies. In this way, secondary pathologies can be avoided by preventing cellular damage and excessive inflammatory responses.

Keywords: Thioldisulfide homeostasis, ischemia-modified albümin, pericardial fluid, coronary artery bypass grafting,

1. BACKGROUND

Coronary artery disease (CAD), which is one of the most common causes of mortality and morbidity all over the world, has many pathophysiological causes and consequences. Reactive oxygen species (ROS) and oxidative stress have negative effects on processes such as the development and acceleration of CAD and plaque formation.[1,2] In particular, ROS, which is formed by the deterioration of molecular and cellular functions, causes oxidative damage above physiological levels.[3] High oxidative stress, which occurs as a result of decreased antioxidants and increased oxidants together with inflammation, has a synergistic effect on the standard risk factors of CAD.[4] The synergistic effect induced by the low antioxidant level and the high oxidant status leads to the initiation of inflammatory cascades and oxidation of low-density lipoprotein

(LDL). Subsequent processes lead to the formation of foam cells from macrophages, differentiation of vascular smooth muscle cells, activation of vascular matrix metalloproteinases, and disruption of the extracellular matrix of the affected area.[5-7] This situation has irreversible consequences for CAD. Therefore, the delicate balance between oxidants and antioxidants is vital in these processes.

The main goal in ROS-mediated biochemical reactions is not to create oxidative stress, but to try to maintain and restore "redox homeostasis".[8] Thiol/disulfide level has critical importance in maintaining and maintaining plasma and intracellular redox homeostasis.[8,9] Thiols, which are the main factor in ensuring the redox balance, have a high sensitivity to oxidation due to the -SH (1 sulfur and 1 hydrogen atom) groups in their structures and interact with almost all physiological oxidants. Because of these properties, they are considered "essential antioxidant buffers".[9-12] In addition to their antioxidant properties, they play a role in many biochemical events such as regulation of protein functions, signal transduction, regulation of transcription factors, and immune response.[12-14]Disulfides, the oxidized form of thiols, are redox-sensitive covalent bonds formed between two thiol groups (sulphydryl atom). Disulfide bond structures formed by ROS oxidation can revert to thiol groups and thus maintain the thiol/disulfide balance. The thiol/disulfide ratio is a new marker used as a measure of thiol and disulfide homeostasis. Thiol/disulfide levels change significantly in the pathogenesis of cardiovascular diseases, diabetes, cancer, and renal failure.[9]

The N-terminal amino end of the albumin molecule, which is an important source of thiol and accepted as the thiol pool of the plasma, is the binding site of metal ions such as Co^{+2}, Ni^{+2}, and Cu^{+2}. In oxidative stress, which occurs in many different conditions such as acidosis, hypoxia, and exposure to free iron and copper, the N-terminus of albumin is modified and its ion-binding ability decreases.[15] This modified form of albumin is called ischemia-modified albumin (IMA).[16] In various coronary syndromes, ischemia, acidosis, hypoxia, and ROS increase caused by decreased coronary blood flow lead to albumin modification and an increase IMA level.[17] IMA levels, which increase in a short time in the early phase of ischemia and in myocardial infarction, are used as a cardiac biomarker in clinical practice.[18,19] IMA, which reflects myocardial ischemia within minutes, shows the degree of short-term oxidative effect.[20] Sinha et al. reported that the sensitivity of the IMA level increased to 95% when used together with electrocardiography and cardiac troponin (cTnT) in acute coronary syndrome.[21]

Foreign material surface, hemolysis, surgical procedure, and reperfusion affect the cellular redox balance in the on-pump coronary artery bypass grafting (CABG) method, which is used for surgical treatment in CAD and performed with the help of cardiopulmonary bypass (CPB). In addition, the high level of molecular oxygen given to the circulatory system during on-pump CABG creates cellular stress and activates the inflammatory system. The resulting stress and inflammatory response affect almost all biochemical reactions by disrupting holistic homeostasis and causing serious damage.[22,23] A shift in the thiol/disulfide redox balance at this stage can have adverse systemic consequences. Because most of the redox-sensitive signal chains respond to changes in the thiol redox state when exposed to ROS.[8] For example, the transcription factor AP-1, which is directly related to the redox state; regulates inflammatory gene expression in response to various stimuli, including cytokines, growth factors, stress, bacterial, and viral infections.[24-26] Nuclear factor-kappa B (NF-ϰB), another transcription factor sensitive to the redox state, plays a role in regulating the expression of many other genes related to cell survival, proliferation, and differentiation in inflammatory and immune responses.[24, 27] Moreover; Signaling pathways such as JNK, p38 MAPK, and amplification of immunological functions are also stimulated according to redox balance.[28] Therefore, detection of thiol/disulfide homeostasis is extremely important in terms of controlling redox-mediated inflammatory signaling pathways during on-pump CABG.

Although there are many studies on thiol/disulfide homeostasis, there are few studies on the relationship between on-pump CABG and thiol/disulfide homeostasis and IMA levels. In addition, such a study related to the subject of pericardial fluid has not been found in the literature. Thanks to this study, it is important to investigate the thiol/disulfide balance and IMA levels in both the pericardial fluid and plasma of the same patient (before and after on-pump CABG) in terms of their secondary effects. In this study, the physiological and biochemical changes of the heart in terms of thiol/disulfide balance were investigated by examining the

pericardial fluid, which is the closest tissue fluid to the heart, and gives accurate information about the heart.

Plasma thiol/disulfide ratio; It can be an easy target for therapeutic intervention by N-acetylcysteine or other thiol compounds. In order to control the oxidative stress that may occur during on-pump CABG, thiol/disulfide homeostasis can be followed to prevent negative situations that may be caused by stress. For this, many treatment strategies can be developed, including the addition of antioxidant substances to the CPB system or intrapericardial drug administration.

In this study, preop and postop thiol/disulfide balance and IMA levels were compared in the plasma of patients undergoing coronary artery bypass surgery. In addition, the thiol/disulfide balance and IMA levels in pericardial fluid were also investigated in this study and their relationship with plasma was evaluated.

2. METHODS

2.1. Study population and processes

A total of 60 patients who underwent coronary artery bypass surgery with on-pump CABG were included in this study. The present study was approved by the local ethics committee (Approval number: 04.07.2022-2022/13/19). All operations were carried out by the same operations team. Exclusion criteria consisted of patients who had a preoperative infection, had a blood product transfusion, received inotropic support, had a history of oxygen support in the last two weeks, and needed postoperative extracorporeal membrane oxygenation (ECMO) support. All procedures were performed under general anesthesia with mild hypothermic cardiopulmonary bypass. Intermittent isothermal blood cardioplegia was used for myocardial protection. General anesthesia was maintained with sevoflurane and intravenous rocuronium was used for neuromuscular blockade.

2.2. Cardiopulmonary bypass management

Standard CPB was performed with mild hypothermia (32°C). After median sternotomy and heparinization (300 IU/kg), CPB was performed with aorto-venous two-stage cannulation. A cross-clamp was placed on the ascending aorta and cardiac arrest was provided with antegrade cardioplegia (10 mL/kg) with high potassium. Continuity of the cardiac arrest was provided with blood cardioplegia given every 20-30 minutes. CPB was established with a roller pump with a membrane oxygenator (Maquet, Getinge Group, Restalt, Germany) and arterial line filter at pump flow rates of 2.2-2.4 L/ min/m^2.

2.3. Pericardial fluid and blood sample collection

Before and after on the CPB, we collected venous blood samples from all patients. The collected samples were centrifuged at 1500 g for 10 min at 4 °C and stored at -80 degC until analysis. In addition, after median sternotomy was performed with standard CPB procedures, the pericardium was opened and the pericardial fluid (PF) was aspirated with a sterile syringe. The aspirated PF (2-5 mL) was then taken into sterile tubes without anticoagulant and placed in an ice-filled container. Afterward, the samples were centrifuged (At 2500 g for 5 min at 4 degC) 2 times and the supernatant phase was separated. Supernatants were stored in RNase-free tubes at -80 degC until assayed. Albumin levels in plasma and PF samples were measured by the biuret method.

2.4. Measurement of thiol/disulfide homeostasis

The thiol/disulfide homeostasis parameters were studied with a new method previously described by Erel et al. First, dynamic disulfide bonds (-S-S)were reduced to reactive thiol groups in the presence of sodium borohydride.[9] Later, total thiol and native thiol (-SH) levels were determined using Ellman reagents.[29] The dynamic disulfide amount was obtained by dividing the difference between the total and native thiol by two. Oxidized thiol, reduced thiol, and thiol-oxidation reduction parameters were calculated according to the formula below. Oxidized thiol [(-S-S-) X 100/ total thiol)], Reduced thiol [(-SH X 100) / total thiol] and Thiol oxidation reduction [(-S-S-) X 100/(-SH)]. Native thiol, total thiol, and disulfide levels were expressed as μmol/L.

2.5. Measurement of IMA

Plasma and PF IMA levels were analyzed using the colorimetric method developed by Bar-Or et al.[30] In the basic principle of the test, 50 μL of cobalt chloride reagent is added to 200 μL of plasma/PF. The mixture is incubated for 10 minutes to form the albumin-cobalt complex. Then, 50 μL (1.5 mg/mL) of dithiothreitol solution is added as a coloring agent and vortexed. Finally, 1.0 mL of 0.9% NaCl is added. The colored complex formed by the addition of NaCl is measured spectrophotometrically at a wavelength of 470 nm. Results are expressed in absorbance units (ABSU).

2.6. Statistical analysis

In assessing the data, SPSS v.25 statistical package program (IBM SPSS Inc, Chicago, IL, USA) has been used. Shapiro-Wilk test was used to control the normal distribution of data. Data with and without normal distribution were expressed as mean±standard deviation and median (range of quarters), respectively. Paired-Samples T-test (In parametric assumptions) and Wilcoxon test (For non-parametric assumptions) were used to investigate the relationship between the two dependent variables. The relationship between the parameters was made using Pearson or Spearman correlation analysis. $p < 0.05$ was regarded as statistically significant.

3. RESULTS

The demographic characteristics of the patients are summarized in Table 1. Twenty-four of the patients were female and 36 were male, with a mean age of 61.38 ± 10.55 years, the height of 164.17 ± 6.82 cm, the weight of 77.42 ± 18.32 kg, and body surface area (BSA) of 1.84 ± 0.23 m^2.

Table 1. Demographic characteristics of patients (n=60)

Demographic findings	**n**	**%**	**Mean ±SD**
Age (Year)	60		61.38±10.55
Gender (Male/Female)	36/24	%60/%40	
Body surface area (m^2)			1.84±0.23
Number of anastomosis	1-2-3-4/4-22-26-8		2.63±0.80
Height (cm)			164.17±6.2
Weight (kg)			77.42±18.2

Table 2 shows the albumin, IMA, and thiol/disulfide homeostasis levels of plasma samples taken before and after CPB. Our results showed that albumin and IMA levels were significantly higher postop compared to preop: 5.32 (0.62), 0.80 ± 0.09, and 4.19 (1.55), 0.71 ± 0.10, respectively; $p < 0.001$, $p < 0.001$.

Table 2. Plasma thiol/disulfide homeostasis in patients having CPB surgery[a]

Variables	**Preop CPB (n = 60)**	**Postop CPB (n = 60)**	**p-value[b]**
Albumin, (gr/dL)	4.19 (1.55)	5.32 (0.62)	<0.001[d]
IMA, (ABSU)	0.71 ± 0.10	0.80 ± 0.09	<0.001[c]
Native thiol (μmol/L)	310.28 ± 64.78	197.38 ± 69.72	<0.001[c]
Total thiol (μmol/L)	365.20 (66.28)	233.18 (81.16)	<0.001[d]
Disulfide bonds (μmol/L)	17.99 (20.01)	15.15 (8.51)	0.001[d]
Reduced Thiol (%)	90.00 (13.63)	86.52 (8.11)	0.686[d]
Oxidized Thiol (%)	4.99 (6.81)	6.90 (3.89)	0.653[d]
Thiol Oxidation-Reduction (%)	5.55 (9.43)	7.82 (5.26)	0.696[d]

CPB, Cardiopulmonary Bypass; IMA, Ischemia Modified Albumin; ABSU, absorbance units

[a]Data are expressed as mean±standard deviation and median (interquartile range) where appropriate.

[b]p <0.05 was considered significant

[c] Obtained from paired samples t -test

[d] Obtained from Wilcoxon test

In comparison, thiol/disulfide parameters, native thiol, total thiol, and disulfide levels were higher and more statistically significant in preop than in postop (respectively, p<0.001, p< 0.001, p=0.001) (Fig. 1).

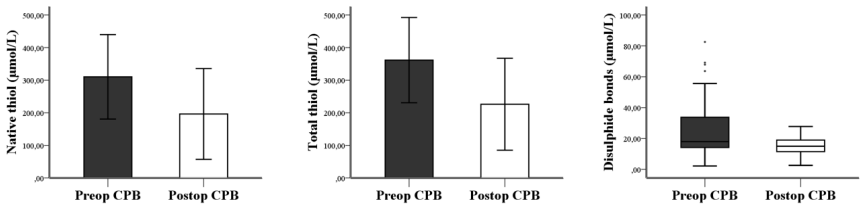

Fig. 1. Plasma native thiol, total thiol, and disulfide bonds levels in preoperative and postoperative CPB (respectively, p <0.001, p <0.001, and p=0.001)

There was no statistical difference between preop and postop in terms of reduced thiol, oxidized thiol and thiol oxidation-reduction (p > 0.05 for all). Table 3 shows the thiol/disulfide parameters, IMA and albumin levels in the pericardial fluid. There was a negative correlation between pericardial fluid IMA and thiol/disulfide parameters (IMA vs. native thiol, r = -0.530, p < 0.001; IMA vs. total thiol, r = -0.552, p < 0.001; IMA vs. disulfide, r = -0.517, p < 0.001). (Fig 2).

Table 3. Pericardial fluid thiol/disulfide homeostasis in patients having CPB surgery[a]

Variables	**CPB (n = 60)**
Albumin, (gr/dL)	2.55 ± 0.73
IMA, (ABSU)	0.81 ± 0.10
Native thiol (µmol/gr protein)	5.41 (3.76)
Total thiol (µmol/gr protein)	7.01 (4.72)
Disulfide bonds (µmol/gr protein)	0.78 (0.67)
Reduced thiol (%)	74.80 ± 7.44
Oxidized thiol (%)	12.59 ± 3.72
Thiol oxidation-reduction (%)	16.36 (11.66)

CPB, Cardiopulmonary Bypass; IMA, Ischemia Modified Albumin; ABSU, absorbance units

[a]Data are expressed as mean±standard deviation and median (interquartile range) where appropriate.

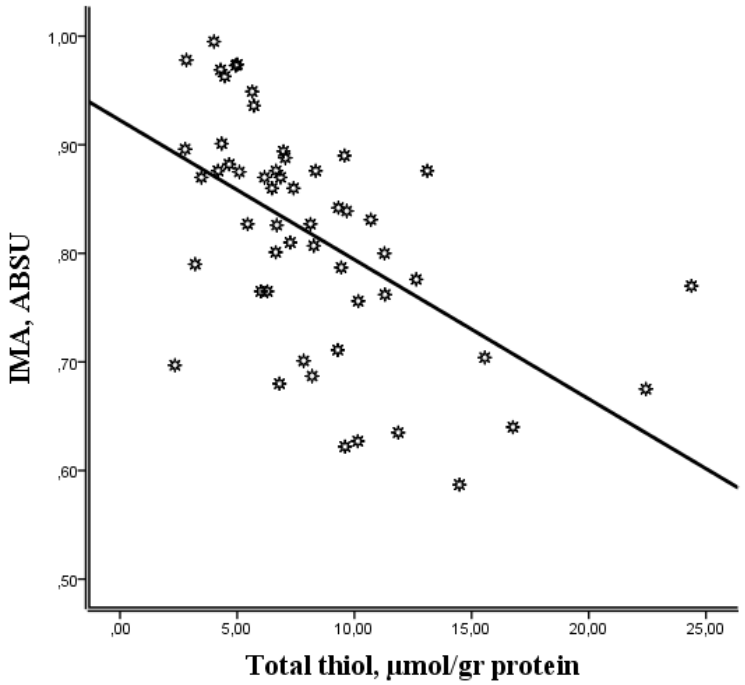

Fig. 2. Correlative relationship between pericardial fluid IMA and Total thiol levels (*r= -0.552, p < 0.001)* .

The results of the Pearson-Spearman correlation analysis investigating the association between pericardial fluid IMA, native thiol, total thiol, and disulfide bonds and serum preop-postop parameters are shown in Table 4. There was no correlation between preop and postop pericardial fluid levels.

Table 4. Pearson-Spearman correlation analysis between pericardial fluid parameters and serum preop-postoperative parameters

Pericardial fluid	**Preop CPB (n = 60)**	**Postop CPB (n = 60)**
IMA *r p*	-0.040 [a] 0.775	-0.047 [a] 0.737
Native thiol *r p*	-0.132 [a] 0.346	-0.040 [a] 0.776
Total thiol *r p*	-0.082 [b] 0.557	0.081[b] 0.559
Disulfide bonds *r p*	-0.078 [b] 0.580	0.173 [b] 0.211

[a] Obtained from Pearson Correlation analysis,[b] Obtained from Spearman Correlation analysis

4. COMMENT

During the CPB performed with an on-pump CABG, tissue perfusion and blood pressure deteriorate, blood flow decreases, and ischemia, acidosis, hypoxia, and ROS increase with the effect of foreign material surface.[31] Oxidative stress caused by all these multifactorial factors increases myocardial damage, triggers inflammatory processes, limits the success of the surgical procedure, and adversely affects the patient's survival or recovery time. Therefore, detection of systemic redox hemostasis before and after on-pump CABG is extremely important for the prognosis of the surgical procedure and the disease. The results obtained in the study show that the levels of native thiol, total thiol, and disulfide decrease after an on-pump CABG. These results are important in terms of minimizing the poor prognostic effects of cardioplegia applied during the on-pump CABG procedure and the subsequent reperfusion period.

The non-specific inflammatory response in the CPB process, which creates a foreign environment outside the body with extracorporeal circulation, shows its negative effects from the first minutes.[32]Cardiac arrest, especially after cardioplegia, causes serious global ischemia in the heart. The increased systemic inflammatory response in this process and the subsequent reperfusion period cause an increase in oxygen-derived free radicals, which can cause myocardial damage and many problems.[33] The primary targets of the formed ROS are the -SH groups of sulfur-containing amino acids (cysteine, methionine) in proteins. Reversible disulfide bonds form from -SH groups oxidized by ROS. This is the first indication of radical-mediated protein oxidation. Evidence has shown that there are significant relationships between changes in thiol/disulfide homeostasis and cardiovascular diseases.[4,33,34]

In some studies, significant positive correlations were found between the peak levels of troponin I—one of the most important cardiac biomarkers—and disulfide levels, disulfide/native thiol, and disulfide/total thiol ratios.[1] Altıparmak et al. reported that the native and total thiol levels were significantly decreased in patients with critical coronary artery disease, and these reductions were associated with the severity of coronary artery disease.[35] These studies show that low native thiol levels are independent predictors of coronary artery disease.

In this study, albumin and IMA levels increased in plasma samples after CPB compared to pre-CPB, while native thiol, total thiol, and disulfide levels decreased. Significant differences were detected between albumin, IMA, and thiol/disulfide homeostasis parameters measured at different times of CPB. Accordingly, plasma native and total thiol levels decreased due to increased oxidative stress during CPB. *In vivo,*ROS played an active role in reducing the thiol level, and oxidative conversion and reduction of thiols to disulfides were performed. Under normal conditions, the disulfide level should increase in response to the decreasing native thiol level. However, the opposite was found in our study. The most important reason for this is that the level of disulfides in the CPB system may have decreased due to adherence to the non-endothelial surface and filters. During CPB, especially since capillary permeability is impaired, fluid flows from the vein to the tissues, and the intravascular fluid decreases. Accordingly, plasma albumin density may have increased after CPB.

Decreased myocardial blood flow causes hypoxia, acidosis, increase in reactive oxygen derivatives and changes in serum albumin, thereby increasing the formation of IMA.[36] Similarly, in our study, plasma IMA levels increased after CPB. The reason for this may be the modification of albumin levels as a result of ischemia, acidosis, hypoxia and ROS increase for many reasons, including impaired tissue perfusion, decreased blood flow or foreign material surface during CPB. Because even the slightest decrease in blood flow can change the level of IMA.[31] A study confirming this information has reported that continuous ventilation during CPB provides benefits for an increase in native and total thiol levels, a decrease in IMA levels, and a shorter hospital stay.[31] Continuous ventilation during CPB reportedly reduces ischemia and provides better inspiratory capacity by reducing lung damage.[37] Ischemia-modified albumin and redox homeostasis can be controlled by reducing ischemia and hypoxia with correct ventilation and oxygenation procedures during CPB.

Considered an ultrafiltrate of plasma, pericardial fluid is also a transudate released from the cardiac interstitium, reflecting the cardiac interstitium's composition and the production of macromolecules in the myocardium.[38,39] This study is the first in the literature to investigate IMA and thiol/disulfide homeostasis in pericardial fluid, support the view that pericardial fluid is plasma ultrafiltrate and provide important information on the matter. The negative relationship between IMA and thiols in the pericardial fluid indicates the effect of ischemia in the pericardium. Rapidly rising IMA levels are used as a cardiac biomarker in the early phase of ischemia and myocardial infarction.[20] Detection of IMA, which reflects ischemia in the myocardium and has a high sensitivity, in the pericardial fluid shows that the pericardial fluid reflects the heart's subclinical condition in coronary artery diseases. However, it is difficult to measure the degree of subclinical conditions in the heart and their effect on the heart, and there is no clear procedure for treatment.

The relationship between albumin, IMA, and thiol/disulfide homeostasis parameters during and after CPB, postoperative complications and the need for inotropic support has not been clarified. One study reported

that thiol levels decreased in acute ischemic strokes and that thiol supplements could reduce neuronal damage associated with stroke and provide recovery. The same study reported that N-acetylcysteine or other thiol providers with antioxidant properties can also be used as a therapeutic intervention in the thiol/disulfide balance.[29,40]

5. CONCLUSION

Determination of IMA and thiol/disulfide homeostasis levels, which are predictive of postoperative complications in on-pump CABG, is important for the success of the surgical procedure and the prognosis of the disease. Redox hemostasis, which is disrupted by the surgical procedure, cardioplegia application, perfusion technique, blood pressure change, non-endothelial surface and anesthesia applications in the on-pump CABG process cause many secondary complications. In the on-pump CABG, cardiac damage can be minimized by making therapeutic supplements with antioxidant properties to the thiol/disulfide balance or by developing biocompatible surfaces.

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