August 2021

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Comparison of serum tumor necrosis factor, superoxide dismutase, and heat shock protein-70 levels during cardiopulmonary bypass and ischemia reperfusion injury after cardiopulmonary bypass in cardiac surgery

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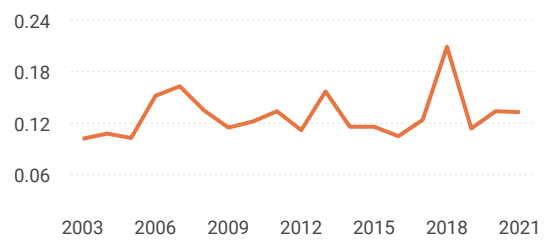

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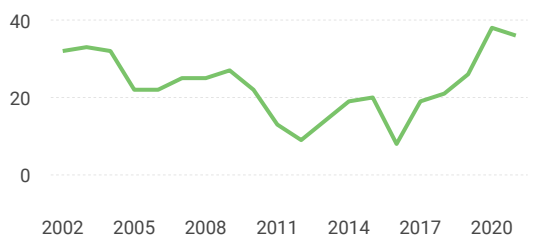

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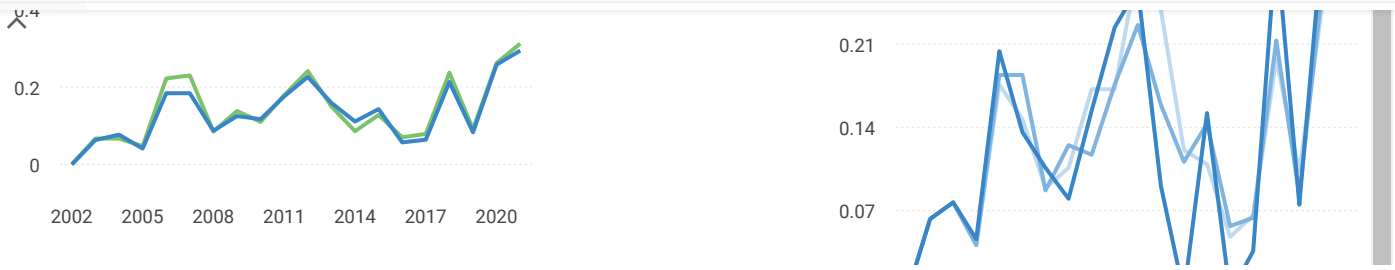

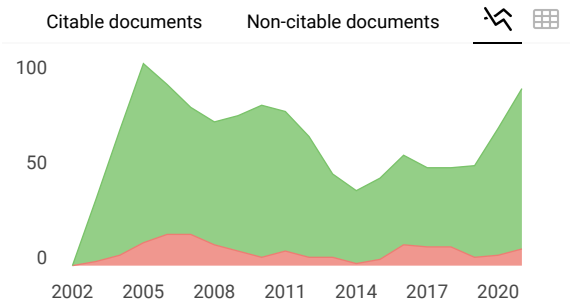

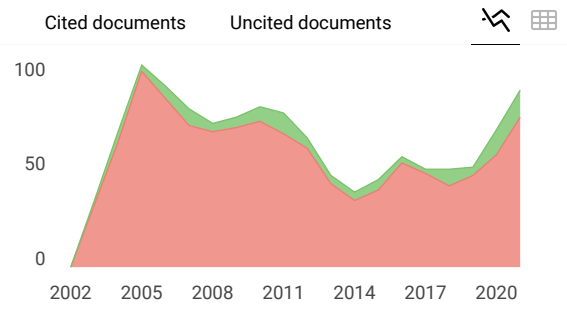

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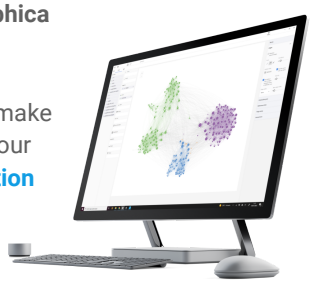

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Crit Care Shock (2021) 24:181-189

Comparison of serum tumor necrosis factor, superoxide dismutase, and heat shock protein-70 levels during cardiopulmonary bypass and ischemia reperfusion injury after cardiopulmonary bypass in cardiac surgery

Teuku Aswin Husain[1,2], Setiawan P[2], Yan Efrata Sembiring[3], Budiono[4]

Abstract

***Objective*: This study aims to determine the comparison between tumor necrosis factor (TNF)-α, superoxide dismutase (SOD), and heat shock protein (HSP)-70 levels during cardiopulmonary bypass (CPB) and ischemia reperfusion injury after cardiopulmonary bypass.**

***Design*: This study was an analytical observational study with a cross sectional design.**

***Setting*: This study was conducted at Dr. Soetomo General Hospital Surabaya. The period of study was from April 2020 to September 2020.**

***Patients and participants*: Population of study was all adult patients who underwent on pump cardiac surgery. Study samples were patients who were included in inclusion criterion. Patients' characteristics were presented as frequency and percentage.**

***Measurement and results*: All interval data with normal distribution were analyzed using T-pair test. Statistical test using the Wilcoxon signed-ranks test (two-tailed) was performed to determine comparison of TNF-α, SOD, and HSP-70 levels during CPB and after CPB. There were 30 subjects who underwent adult cardiac surgeries including coronary artery bypass graft (CABG), valve, and double procedures. According to statistical test, there was a significant increase of TNF-α, SOD, and HSP-70 levels during cardiopulmonary bypass compared to after cardiopulmonary bypass with p-value <0.05. Pearson correlation test was performed to determine the correlation between elevated levels of TNF-α, SOD, HSP-70 during CPB impact. There was significant correlation between TNF-α and SOD (p<0.05), and also between SOD and HSP-70 (p<0.05).**

***Conclusion*: Our study showed that CPB impact significantly contributes to the increase of TNF-α, SOD, and HSP-70 levels compared to after CPB in patient undergoing on pump cardiac surgeries.**

Key words: Cardiopulmonary bypass, TNF-α, SOD, HSP-70.

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Introduction

The two most important insults that influence the occurrence of cardiac problem after cardiopulmonary bypass (CPB) during cardiac surgery are impact during CPB and ischemia-reperfusion injury after CPB. (1)

Ischemia-reperfusion injury may induce the activation of many inflammatory mediators during oxidation, which are then released into systemic circulation. (2) Cardiopulmonary bypass, due to the friction of blood through the artificial blood pipe and its laminar blood flow, also induces the production of many inflammatory substances. (3)

Tumor necrosis factor (TNF)-α is an inflammatory cytokine that has a unique main biological activity to cause organ damage during cardiac surgery. (4)

The increase in TNF-α levels is caused by mechanical factors and the biomolecular impact of CPB. (5) The increase in TNF-α can cause a decrease in the structural function of the heart muscle, initiate inflammation, increase the ability of macrophages in phagocytosis or chemotaxis in tissues, and trigger the spread of oxygen free radicals into the systemic through the binding of $O2^-$ and tissue cell apoptosis. (6)

During CPB and ischemia reperfusion injury after CPB, the production of reactive oxygen species (ROS) increases, this triggers an additional amount of superoxide dismutase (SOD) as a buffer mechanism to protect cells against ROS. (7)

Excessive ROS may also induce hazard response to the cells, among them are vasodilatation due to activation of endothelial derived-relaxing factor (EDRF) by superoxide cell membrane lysis caused by accumulation process of hydroxyl peroxide and cell protein denaturation by hydrogen chloride and nitric oxide. (8,9)

The cytoprotective effect of heat shock protein (HSP-70) during cardiac surgery will neutralize the impact of increased TNF-α and oxidative stress, which can certainly protect the organ from possible biological and mechanical damage. (10) Apart from reducing myocardial oxidative stress and excessive calcium, HSP-70 also regulates tissue cell apoptosis-related proteins. (11)

Our study's objective was to determine whether impact during CPB or ischemia-reperfusion injury after CPB contribute more to the increase of inflammatory mediators and protective cell substances during on pump cardiac surgeries. The sample size was measured by using the sample size formula. Furthermore, a statistical test was conducted to assess the validity of the research hypothesis.

Materials and methods

The design of this research was a cross sectional observational analytic research. After getting permission from the Research Ethics Committee of Dr. Soetomo General Hospital, the research was carried out immediately. Sampling of this research was conducted in the Operating Room of the Integrated Cardiac Services Building Dr. Soetomo General Hospital Surabaya during the period April to September 2020. The research population were adult patients that underwent open heart surgery. Samples were taken consecutively that met the inclusion criterion, which was non-congenital adult patients aged 30-65 years. Meanwhile, the exclusion criteria were congenital heart defects, emergency surgery or redo, high vasoactive-inotropic score (VIS), ejection fraction (EF)<40%, and patients with low output syndrome or organ dysfunction. The sample size was calculated based on the sample size formula, which resulted in minimum of 20 samples.

The anesthetic technique in this research was based on the underlying cardiac pathophysiology of the disease. The principle of opioid base anesthesia was the basis for selecting anesthetics technique. During the cardiac surgery procedure, arterial blood samples were taken for three periods, those were pre-CPB before induction of anesthesia, during CPB cooling period after 60 minutes of full flow, and during sternal closure after CPB. Furthermore, the blood sample was inserted into the reagent tube and collected at the Clinical Pathology Laboratory, 5th floor of Dr. Soetomo General Hospital. Assessment of TNF-α, SOD, and HSP-70 levels were carried out using enzyme-linked immunosorbent assay (ELISA) kits. Furthermore, the data were collected in tabular form and research documentation.

The data obtained were in the form of nominal levels of TNF-α, SOD, and HSP-70 at pre CPB, during CPB, and after CPB. Furthermore, statistical tests of level changes and correlation of TNF-α, SOD, and HSP-70 levels were carried out in pre CPB, during CPB, and after CPB. A two-tailed Wilcoxon signed rank statistical test was performed to analyze the increase levels of TNF-α, SOD, and HSP-70 during cardiac surgery. Meanwhile, statistical correlation tests were carried out using Pearson's correlation. The level of significance was obtained using an odds ratio with a 95% confidence level. Statistical significance was assessed as significant if the p-value <0.05.

Results

From 30 patients admitted to this study, 4 patients were dropped out in this research because of low output after CPB and long CPB time. A total of 26 patients were enrolled in this study, it can be seen in **Table 1**. As many as 46.2% were cases of coronary artery bypass grafting (CABG), while 53.8% were non-CABG, which included mitral (23%), aortic (7.7%), mitral valve replacement plus CABG (7.7%), and mitral valve replacement plus tricuspid valve repair (15.3%) as seen in **Figure 1**.

Interpretation of the normality test was done by using Shapiro-Wilk. It was found that the distribution of the research samples was normally distributed at pre CPB, during CPB, and after CPB with $p<0.05$. The statistical test using Wilcoxon signed ranks compared increased levels of TNF-α, SOD, and HSP-70 during cardiac surgery. Because of the difference in nominal parameters of the baseline TNF-α, SOD, and HSP-70 levels, we used statistical analysis correlation to define those levels.

Increased levels of TNF-α, SOD, and HSP-70 during CPB compared to pre-CPB was statistically significant ($p<0.05$) based on this research. However, increased levels of TNF-α, SOD, and HSP-70 after CPB compared to during CPB was not significant with $p>0.05$. Comparison of significance of each parameter and p-value during cardiac surgery can be seen in **Tables 2, 3,** and **4**.

The correlation percentage of increased levels of TNF-α, SOD, HSP-70 during CPB is shown in **Table 5**. The percentage of increased levels of TNF-α and SOD during CPB compared to pre CPB had a significant correlation with $p<0.05$. Meanwhile, the percentage of increased levels of TNF-α and HSP-70 expression during CPB compared to pre CPB had insignificant correlation with $p>0.05$.

Discussion

Organ dysfunction arising from post-cardiac surgery is not separable from the impact of CPB in causing inflammation and oxidative stress during CPB. (12-17) There are two parallel paths that cause damage molecularly. The two pathways are different sequence in causing tissue cell damage. In the cardiopulmonary bypass pathway, tissue cell damage is caused by activation of the inflammatory cascade, that is to mention complement activation and leukocyte activation, while in the ischemia reperfusion pathway, tissue cell damage is caused by anaerobic metabolism and an increase in the number of free radicals (ROS). (18-21) The two pathways can overlap and join the chain of more severe tissue cell damage. (22) The differences in the baseline values for the TNF-α, SOD, and HSP 70 parameters are caused by individual variations, comorbid diseases, age, and the impact of heart disease itself. (23,24)

The statistical significance of the increase in TNF-α levels during CPB to pre CPB due to the interaction of CPB with the patient's blood circulation, surgical shear injury, impaired intestinal permeability, inadequate hypothermic distribution, hemodilution, and tissue cell hypoperfusion during CPB can lead to an increase in TNF-α during the CPB. (25) On a different side, the significance of the increase in TNF-α after CPB compared to during CPB was not significant with $p>0.05$ in this research. The low statistical significance can be explained due to the fact that in the early phase after CPB, there is not much increase in TNF-α. The factors that cause this condition include the absence of CPB interaction with patient, improvement of inflammation due to improved macro-circulation or hypoperfusion from previous disease and variable peak timing of reperfusion ischemic injury. Some literature mentions 6 hours post surgery, on the other hand there are those who have reported the injury more than 24 hours post surgery. (26,27)

The elevated levels of SOD during CPB compared to pre CPB in this research was statistically significant with $p<0.05$. The increase in SOD levels is the body's response to the increasing number of free radicals or ROS caused by the impact of CPB. According to Luyten et al., during cardiac surgery there was an increase in glutathione levels by 40% and 30% SOD, which then returned to normal after 24 hours postoperatively. (28) ROS recirculation mediated by an increase in TNF-α levels during CPB will cause ROS levels to remain elevated in the blood. (29) It was proven in this research that changes in SOD followed changes in TNF-α levels during CPB. Increased levels of SOD acts as antioxidants, which protect cellular components from being oxidized by ROS during cardiac surgery. (30)

The impact of ischemia reperfusion after CPB on changes of SOD levels after CPB compared to during CPB did not have statistical significance. This may be due to adequate post-CPB circulatory performance, which is able to avoid inflammatory stress and oxidative stress. There was decreased role of TNF-α post CPB, and the use of antioxidant adjuvant drugs, for example mannitol, propofol, heparin, inhalation anesthetics, and the use of ultrafiltration during CPB. (31)

Increased expression of HSP-70 during CPB compared to pre-CPB had statistical significant in this research. The increase in HSP-70 expression during CPB is caused by cytoprotective effect of HSP, which increases the activity of inflammatory mediators, some of which are an increase in TNF-α levels, an increase in oxidative stress, and the impact of CPB on damage to patient tissue cells. (32) Meanwhile, the increase of HSP-70 expression after CPB compared to during CPB did not have a statistical significance. The insignificant changes in HSP-70 expression after CPB are caused by an improvement in the inflammatory process post CPB, an improvement in systemic perfusion due to proper cardiac correction, and the absence of a significant increase in free radical stress. According to Hampton et al., the increase in HSP-70 expression is largely determined by the duration of cardioplegia administration and reperfusion. (33)

Initial hypothermia during CPB does not appear to have much effect on changes in the elevated levels of TNF-α, SOD, and HSP-70. Meanwhile, the impact of cross clamp duration greatly influenced the increase of these three parameters during cardiac surgery with $p<0.05$.

The correlation between elevated levels of TNF-α and SOD during CPB compared to pre CPB had statistical significance, but not with HSP-70. The closed association of increased oxidative stress with inflammation might occur during CPB, whereas the cytoprotective effect of HSP-70 limited the increase in TNF-α based on this research. The correlation of elevated levels between SOD and HSP-70 during CPB compared to pre CPB also had statistical significance. Closed correlation of SOD and HSP-70 during CPB are caused by defensed mechanism against threatening inflammation and stress oxidative during CPB. (34)

Inflammation and oxidative stress can cause increased levels of TNF-α as inflammatory precursor, while both SOD and HSP-70 act as anti-inflammatory agents during CPB. Elevated levels of these three substances are related one another.

The advantage of our research is that this research investigated the combined role of inflammatory factor TNF-α with the anti-inflammatory factors SOD and HSP-70. However, this research did not yet have homogenous cardiac surgery specifications. Furthermore, more studies with larger sample size are necessary to further support these data.

Conclusion

Open heart surgery in this research provided vivid picture of the impact of cardiopulmonary bypass on the increase in inflammatory mediators, oxidative stress, and the body's response to these changes. The impact of CPB caused an increase in parameter levels and the correlation percentage of TNF-α, SOD, and HSP-70, which had statistical significance with $p<0.05$. The causes of the increase in these parameters were due to the inflammatory process and oxidative stress during CPB. The increase in TNF-α, SOD, and HSP-70 parameters during CPB in this research had a very closed synergistic relationship during cardiopulmonary bypass. Therefore, inflammation and oxidative stress were linked in the chain of events that occured during CPB according to this research.

Acknowledgments

The authors declared no potential conflicts of interests with respect to the research, authorship, and/or publication of this article.

Table 1. Patient demographic

No.	Parameter	Variable	Amount	Percentage
1	Age (years)	30-39	9	34.6%
		40-49	5	19.2%
		50-59	6	23.1%
		60-69	6	23.1%
2	Gender	Male	18	69.2%
		Female	8	30.8%
3	Comorbid	Without comorbid	3	11.5%
		Hypertension	9	34.6%
		Diabetes	5	19.3%
		Smoker	8	30.8%
		Other	1 (obese)	3.8%
4	Type of surgery	CABG	12	46.2%
		Aorta	2	7.7%
		Mitral	6	23%
		Mitral+CABG	2	7.7%
		Mitral+TV repair	4	15.3%
5	Baseline (pre CPB)			
	- TNF-α	Normal range	17	65.3%
		More than normal	9	34.7%
	- SOD	Normal range	19	73%
		More than normal	7	27%
	- HSP	Normal range	26	100%
		More than normal	0	0%

Legend: CPB=cardiopulmonary bypass; TNF=tumor necrosis factor; SOD=superoxide dismutase; HSP=heat shock protein; CABG=coronary artery bypass grafting; TV=tricuspid valve.

Table 2. Comparison of increased levels of TNF-α during cardiac surgery

	Positive rank (percentage of the amount)	p-value*
TNF-α changes during CPB compared to pre CPB	88%	0.000
TNF-α changes after CPB compared to during CPB	50%	0.770

Legend: TNF=tumor necrosis factor; CPB=cardiopulmonary bypass.
*$p<0.05$ was statistically significant.

Table 3. Comparison of increased levels of SOD during cardiac surgery

	Positive rank (percentage of the amount)	p-value*
SOD changes during CPB compared to pre CPB	96.1%	0.000
SOD changes after CPB compared to during CPB	53.8%	0.679

Legend: SOD=superoxide dismutase; CPB=cardiopulmonary bypass.
*p<0.05 was statistically significant.

Table 4. Comparison of increased levels of HSP-70 during cardiac surgery

	Positive rank (percentage of the amount)	p-value*
HSP-70 changes during CPB compared to pre CPB	92.3%	0.000
HSP-70 changes after CPB compared to during CPB	42.3%	0.330

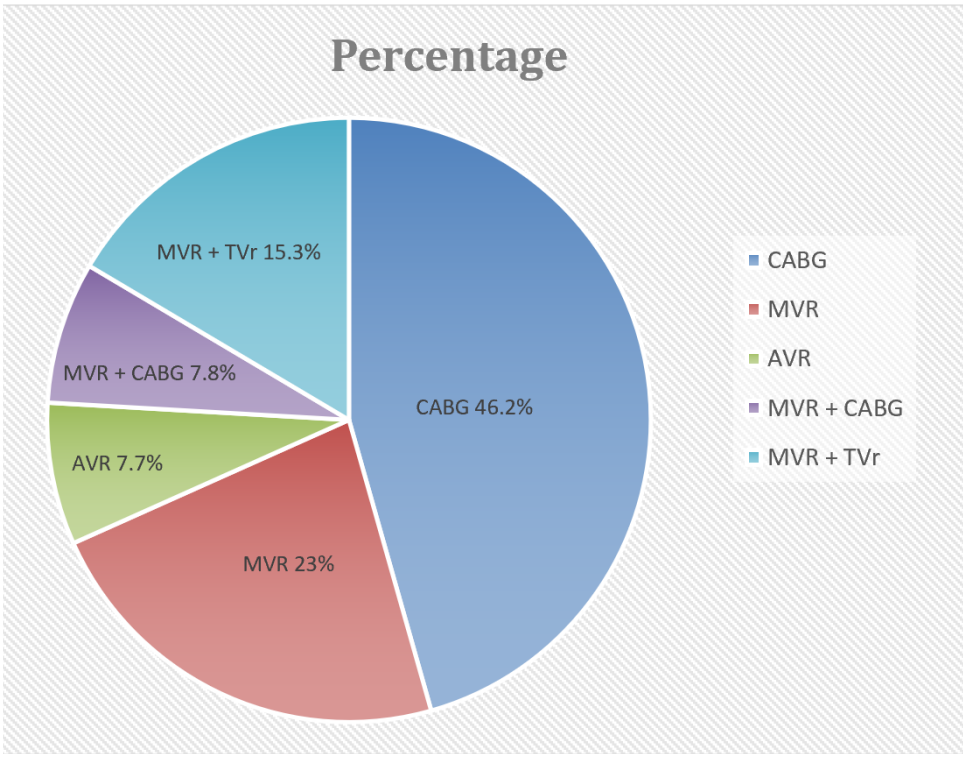
Legend: HSP=heat shock protein; CPB=cardiopulmonary bypass.
*p<0.05 was statistically significant.

Table 5. The correlation of percentage increased levels of TNF-α, HSP-70, and SOD during CPB

Pearson correlation CPB to pre CPB	p-value*		
	%Δ TNF-α	%Δ SOD	%Δ HSP-70
TNF-α		0.017	0.314
SOD	0.017		0.000
HSP-70	0.314	0.000	

Legend: TNF=tumor necrosis factor; HSP=heat shock protein; SOD=superoxide dismutase; CPB=cardiopulmonary bypass; %Δ=percentage increased level.
*p<0.05 was statistically significant.

Figure 1. Types of heart surgery



Legend: MVR=mitral valve replacement; TVr=tricuspid valve repair; CABG=coronary artery bypass grafting; AVR=aortic valve replacement.

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