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Association Between Cardiopulmonary Bypass-Induced Sirtuin-1 Suppression and Apoptosis

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ABSTRACT

Objectives: The aim of this study is to investigate, at the molecular level, the effect of cardiopulmonary bypass (CPB) on Sirtuin-1 levels, an epigenetic-metabolic regulatory protein, and the relationship between this change and Caspase-3, one of the key executor molecules of cellular apoptosis.

Methods: Patients undergoing open heart surgery under CPB were included in the study. Sirtuin-1 and Caspase-3 levels were measured in venous blood samples taken from patients during the preoperative, intraoperative, and postoperative periods. The Wilcoxon Signed Ranks test was used to analyze differences between time points.

Results: Sirtuin-1 levels decreased significantly during the intraoperative period compared to preoperative values ($Z= -6.212$, $P<0.001$). Similarly, postoperative Sirtuin-1 levels were significantly lower compared to both the preoperative ($Z= -6.229$, $P<0.001$) and intraoperative periods ($Z= -6.186$, $P<0.001$). Caspase-3 levels showed a significant increase in the intraoperative period compared to the preoperative period ($Z= −6.262$, $P<0.001$). Postoperative Caspase-3 levels were significantly higher than both the preoperative ($Z= -6.196$, $P<0.001$) and intraoperative periods ($Z= -6.203$, $p < 0.001$).

Conclusions: These findings indicate that CPB suppresses circulating Sirtuin-1 levels and that this suppression is associated with increased apoptosis. CPB-induced Sirtuin-1 inhibition may be one of the molecular mechanisms of surgical-related cellular damage. Sirtuin-1 may be considered a potential molecular target for preventing CPB-related myocardial and systemic damage.

Keywords: Cardiopulmonary Bypass, Sirtuin-1, Caspase-3, Apoptosis, Molecular Perfusion

Cardiopulmonary bypass (CPB) is a fundamental life-supporting technology in open-heart surgery; however, oxidative stress, inflammation, and energy imbalance that develop during this process cause damage at the cellular level [1]. Silent Information Regulator 2 Homolog 1 (Sirtuin-1 / SIRT1), an important regulator of intracellular energy metabolism, is notable for its functions in reducing oxidative stress, protecting mitochondrial function, and slowing cellular aging [2]. Changes in Sirtuin-1 levels during CPB are thought to be decisive for postoperative organ function and the recovery process. Therefore, examining the biochemical changes exhibited by Sirtuin-1 in response to CPB will contribute to redefining perfusion science not only in terms of systemic circulation but also in terms of maintaining cellular homeostasis at the molecular level [3].

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CPR, while an indispensable component of open-heart surgery, triggers complex biological processes associated with systemic inflammatory response, oxidative stress, and cellular damage. During CPB, factors such as contact of blood with non-physiological surfaces, surgical trauma, hypothermia, and ischemia-reperfusion injury trigger complement activation and pro-inflammatory cytokine release, thereby increasing the systemic inflammatory response [4, 5]. The same conditions contribute to an increase in reactive oxygen species production, leading to insufficient endogenous antioxidant capacity and elevated oxidative stress; this condition is associated with postoperative organ dysfunction. [6]. This pro-inflammatory and oxidative environment activates cellular stress responses, paving the way for the triggering of apoptotic pathways, particularly in myocardial and other organ tissues [7]. These mechanistic findings demonstrate that CPB not only achieves hemodynamic goals but also affects the balance between life and death at the molecular level.

Apoptosis is a programmed cell death mechanism that plays a fundamental role in maintaining cellular homeostasis and is closely associated with myocardial dysfunction, acute organ damage, and postoperative complications following cardiac surgery. Caspase-3, which plays a central role in the execution of the apoptotic process, is the common final effector of both intrinsic and extrinsic apoptotic pathways, and its increased circulating levels are considered a biochemical marker of systemic cellular damage. Inflammation and oxidative stress associated with CPB have been reported to trigger apoptosis by increasing caspase-3 activation; however, the higher-level regulatory mechanisms of these processes have not yet been fully elucidated [7-9].

In recent years, Sirtuin-1 has attracted attention as a critical molecular sensor in the regulation of the cellular stress response. Sirtuin-1, a nicotinamide adenine dinucleotide (oxidized form) (NAD^+)-dependent deacetylase, has regulatory effects on mitochondrial function, inflammation, oxidative stress response, and cellular life–death balance. Experimental and clinical studies have shown that Sirtuin-1 exhibits anti-inflammatory and anti-apoptotic properties, particularly supporting cell survival under oxidative stress conditions. Decreased Sirtuin-1 activity has been associated with increased inflammation and apoptosis [10-13].

It has been suggested that systemic inflammation and redox imbalance developing during CPB may have an inhibitory effect on Sirtuin-1 expression and activity. However, in humans, changes in circulating Sirtuin-1 levels, particularly during the perioperative period, and their relationship with apoptotic markers have been evaluated in a limited number of studies. In this context, elucidating the effect of CPB on Sirtuin-1 and its possible relationship with the apoptotic response may contribute to a better understanding of the molecular mechanisms of CPB-related cellular damage [14, 15].

Caspase-3, which plays a central role in the execution phase of apoptosis, is one of the primary effector caspases activated under cellular stress conditions. Increased pro-apoptotic signals resulting from stimuli such as inflammation, oxidative stress, and ischemia-reperfusion injury lead to Caspase-3 activation, causing the cellular death process to enter its irreversible phase. It has been reported that the systemic inflammatory response and oxidative stress environment that arise during CPB trigger Caspase-3-mediated apoptotic pathways and that this contributes to myocardial and extracardiac cellular damage. In this context, Caspase-3 is considered an important apoptotic marker in the assessment of cellular damage associated with CPB [7, 9, 16, 17].

The aim of this study is to evaluate changes in circulating Sirtuin-1 and caspase-3 levels in patients undergoing CPB during the preoperative, intraoperative, and postoperative periods using the ELISA method, and to investigate the relationship between CPB-induced Sirtuin-1 suppression and increased apoptosis. This study aims to shed light on the molecular basis of cellular stress and apoptotic response associated with CPB, thereby contributing to the development of targeted protective strategies in the future.

METHODS

In this prospective clinical and translational molecular medicine study, changes in circulating Sirtuin-1 levels during the perioperative period in patients undergoing

CPB and the relationship between these changes and the caspase-3-mediated apoptotic response were evaluated using the ELISA method.

Ethical Dimension of the Research

Approval for this prospective study was obtained from the institutional administration and the Harran University Clinical Research Ethics Committee (Date: 17.11.2025; Approval No: HRÜ/25.18.33). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Prior to enrollment, written informed consent was obtained from all participants after providing detailed information regarding the purpose, procedures, and potential risks of the study. Blood samples were collected using existing vascular access without any additional invasive intervention, and patient confidentiality was strictly maintained throughout the study. All data were anonymized prior to analysis.

Data Collection Method

A total of 50 consecutive patients undergoing cardiac surgery with CPB and without planned additional surgical procedures were prospectively included in the study. The demographic and clinical data of the patients included in the study were systematically recorded [age, gender, height, weight, body surface area (BSA), flow, aortic cross-clamp time, total perfusion time, and type of surgery performed (number of coronary artery bypass grafts)]. Venous blood samples were collected from patients at three different time points: preoperatively before anesthesia induction, intraoperatively following aortic cross-clamping, and during the weaning phase from CPB, each sample being 10 mL. Blood samples were obtained using existing central venous catheters and the heart-lung machine manifold; no additional invasive procedures were performed on the patients. Circulating Sirtuin-1 and caspase-3 protein levels were analyzed from the collected blood samples using the ELISA method, and the obtained data were evaluated using appropriate statistical methods.

ELISA Analysis

Venous blood samples were centrifuged at 3000 rpm for 10 minutes at 4 °C after clotting to separate the serum. The serum samples obtained were stored at –80 °C until analysis. Samples were thawed only once prior to analysis and were not refrozen. Circulating Sirtuin-1 and caspase-3 protein levels were measured using a human serum-specific ELISA method according to the manufacturer's instructions. The minimum detectable dose of Sirtuin-1 in human serum was 0.28 ng/mL, with a typical range of 0.78–50 ng/mL.

Inclusion and Exclusion Criteria

Inclusion Criteria: Patients aged 20–85 years who were scheduled to undergo elective cardiac surgery with CPB and who provided informed consent following ethical committee approval were included in this study. All patients underwent surgery using the standard CPB protocol without additional surgical procedures.

Exclusion Criteria: Patients who received amiodarone therapy in the preoperative period, those with a history of atrial fibrillation, patients undergoing emergency cardiac surgery, and patients scheduled for additional major cardiac surgery such as aortic aneurysm or aortic dissection were excluded from the study. Additionally, patients with active infection, chronic or active respiratory disease such as pneumonia or chronic obstructive pulmonary disease (COPD), known systemic inflammatory or autoimmune disease, active malignancy, chronic corticosteroid or immunosuppressive therapy, previous cardiac surgery (redo) patients, individuals undergoing chronic hemodialysis treatment, those with hematological diseases, and patients with severe liver dysfunction were excluded from the study.

Statistical Analysis

Patient data collected within the scope of the study were analyzed using the IBM Statistical Package for the Social Sciences 25 (IBM SPSS Statistics 25®) software package (IBM Corporation, Armonk, NY, USA). The sample size was determined based on previous similar studies and power analysis. A minimum power of 80% and a significance level of 0.05 were considered sufficient to detect statistically meaningful differences between groups. Means and standard deviations were calculated for continuous and ordinal data. The Kolmogorov Smirnov test and Shapiro-Wilk test were used to assess normality of distribution (the Kolmogorov–Smirnov test was used

because the number of patients was over 30). Comparemeans (Paired-sample T Test) and Nonparametric test (2Related Samples>Willcoxon) tests were used to evaluate normal and non-normally distributed data, respectively, for the comparison of the same parameters before, during, and after surgery. Frequency and percentage analyses were performed for nominal data. A P value of less than 0.05 was considered statistically significant.

RESULTS

A total of 50 patients were included in the study. Forty-four percent (n=22) of patients were female, and 56% (n=28) were male. When surgical procedures were evaluated, 10% (n=5) of patients underwent coronary artery bypass grafting (CABG)×1, 16% (n=8)underwent CABG×2, 40% (n=20)underwent CABG×3, 24% (n=12) underwent CABG×4, and 10% (n=5) underwent CABG×5 surgery. The number of cases valid for all variables was determined as 50 (Table 1).

The ages of the patients included in the study ranged from 42 to 76 years, with an average age of 61.18±7.23 years. The patients' height ranged from 1.50 to 1.85 m, with an average of 1.66±0.08 m. Body weight ranged from 55 to 103 kg, and the average value was calculated as 78.62±13.39 kg. Body surface area (BSA) ranged from 1.50 to 2.20 m², with an average of 1.86±0.18 m². The average flow rate used during CPB was determined to be 4476.2±420.9 mL/min. The aortic cross-clamp time ranged from 16 to 100 minutes, with an average of 52.84±17.22 minutes. The total perfusion time ranged from 53 to 167 minutes, with an average of 86.08±21.96 minutes (Table 1).

In the 50 patients included in the study, Sirtuin-1 levels ranged from 3.80 to 3.90 ng/mL in the preoperative period, with a mean of 3.85±0.02 ng/mL. Intraoperative Sirtuin-1 levels ranged from 2.88 to 3.00 ng/mL, with a mean of 2.94±0.03 ng/mL. Postoperative Sirtuin-1 levels ranged from 2.40 to 2.56 ng/mL, with a mean of 2.48±0.03 ng/mL. Caspase-3 levels ranged from 145.40 to 145.80 pg/mL in the preoperative period, with a mean of 145.60±0.04 pg/mL. During the intraoperative period, Caspase-3 levels ranged from 198.20 to 198.40 pg/mL, with an average of 198.30±0.03 pg/mL. In the postoperative period, Caspase-3 levels ranged from 236.80 to 237.00 pg/mL,

TABLE 1. Demographic and Perioperative Characteristics of the Patients (n=50)

Categorical Variables		Frequency	Percent	Valid Percent	Cumulative Percent
Gender	Female	22	44.0	44.0	44.0
	Male	28	56.0	56.0	100.0
Operation	CABG×1	5	10.0	10.0	10.0
	CABG×2	8	16.0	16.0	26.0
	CABG×3	20	40.0	40.0	66.0
	CABG×4	12	24.0	24.0	90.0
	CABG×5	5	10.0	10.0	100.0
Continuous Variables		**Minimum**	**Maximum**	**Mean**	**Std. Deviation**
Age (year)		42.00	76.00	61.180	7.232
Height (m)		1.50	1.85	1.659	0.081
Weight (kg)		55.00	103.00	78.620	13.390
BSA (m^2)		1.50	2.20	1.861	0.180
Flow (L/min)		3670.00	5290.00	4476.200	420.911
Cross clamp time (min)		16.00	100.00	52.840	17.220
Total perfusıon time (min)		53.00	167.00	86.080	21.959

BSA, body surface area; CABG, coronary artery bypass grafting.

TABLE 2. Patients' Sirtuin-1 and Caspase 3 Levels Over Time

	Descriptive Statistics (n=50)			
	Minimum	Maximum	Mean	Std. Deviation
Preoperative Sirtuin-1 (ng/mL)	3.80	3.90	3.850	0.015
Intraoperative Sirtuin-1 (ng/mL)	2.88	3.00	2.940	0.025
Postoperative Sirtuin-1 (ng/mL)	2.40	2.56	2.480	0.026
Preoperative Caspase 3 (pg/mL)	145.40	145.80	145.600	0.043
Intraoperative Caspase 3 (pg/mL)	198.20	198.40	198.302	0.027
Postoperative Caspase 3 (pg/mL)	236.80	237.00	236.900	0.033

with an average of 236.90±0.03 pg/mL (Table 2).

Since the data were found not to follow a normal distribution in the normality analysis, the temporal change in Sirtuin-1 levels was evaluated using the Wilcoxon Signed Ranks test. Intraoperative Sirtuin-1 levels showed a significant difference compared to the preoperative period ($Z= -6.212$, $P<0.001$). Postoperative Sirtuin-1 levels showed a significant difference compared to the preoperative period ($Z= -6.229$, $P<0.001$). In addition, a statistically significant difference was found between postoperative and intraoperative Sirtuin-1 levels ($Z= -6.186$, $P<0.001$) (Table 3).

Since the data were found not to follow a normal distribution in the normality analysis, the temporal change in Caspase-3 levels was evaluated using the Wilcoxon Signed Ranks test. Intraoperative Caspase-3 levels showed a significant difference compared to the preoperative period ($Z= -6.262$, $P<0.001$). Postoperative Caspase-3 levels showed a significant difference compared to the preoperative period ($Z= -6.196$, $P<0.001$). Furthermore, a statistically significant difference was found between postoperative and intraoperative Caspase-3 levels ($Z= -6.203$, $P<0.001$) (Table 4).

DISCUSSION

This study demonstrated that CPB significantly suppressed circulating Sirtuin-1 levels and that this suppression was associated with increased apoptosis. The significant decrease in Sirtuin-1 levels detected during the intraoperative and postoperative periods compared to the preoperative period suggests that the oxidative stress, inflammatory response, and metabolic imbalances caused by CPB exert an inhibitory effect on epigenetic-metabolic regulatory mechanisms. Considering the anti-apoptotic and cytoprotective effects of Sirtuin-1, this suppression may pave the way for the activation of apoptotic pathways under cellular stress conditions. Indeed, the significant increase observed in Caspase-3 levels during the same time period indicates the activation of executive apoptosis pathways and supports a possible causal relationship between Sirtuin-1 suppression and apoptosis. It is known that Sirtuin-1 supports cell survival by deacetylating transcription factors such as Tumor Protein p53 (p53), Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells (NF-κB), and Forkhead Box O; therefore, decreased Sirtuin-1 activity during CPB may contribute to the

TABLE 3. Comparison of Sirtuin-1 Levels Across Preoperative, Intraoperative, and Postoperative Periods

	Test Statistics[a]		
	Intraoperative Sirtuin-1 - Preoperative Sirtuin-1	Postoperative Sirtuin-1 - Preoperative Sirtuin-1	Postoperative Sirtuin-1 - Intraoperative Sirtuin-1
Z	-6.212[b]	-6.229[b]	-6.186[b]
Asymp. Sig. (2-tailed)	**<0.001**	**<0.001**	**<0.001**

[a]Wilcoxon Signed Ranks Test, [b]Based on positive ranks.
Statistically significant P-values are shown in bold.

TABLE 4. Comparison of Caspase-3 Levels Across Preoperative, Intraoperative, and Postoperative Periods

Test Statistics[a]			
	Intraoperative Caspase 3 - Preoperative Caspase 3	Postoperative Caspase 3 - Preoperative Caspase 3	Postoperative Caspase 3 - Intraoperative Caspase 3
Z	-6.262[b]	-6.196[b]	-6.203[b]
Asymp. Sig. (2-tailed)	**<0.001**	**<0.001**	**<0.001**

[a]Wilcoxon Signed Ranks Test, [b]Based on negative ranks.
Statistically significant P-values are shown in bold.

uncontrolled progression of the Caspase-3-mediated apoptotic process. These findings reveal that CPB causes cellular damage not only at the hemodynamic and inflammatory levels, but also at the epigenetic and molecular levels, and suggest that the Sirtuin-1 – Caspase-3 axis may play a critical role in understanding the molecular mechanisms of CPB-related organ damage.

During CPB, factors such as contact of blood with non-physiological surfaces, ischemia–reperfusion injury, hemodilution, and oxidative stress trigger a systemic inflammatory response. These processes result in mitochondrial dysfunction and redox imbalance at the cellular level, paving the way for the activation of apoptotic pathways [18]. In our study, the increase observed in caspase-3 levels after CPB can be considered a biochemical reflection of systemic apoptotic activation associated with CPB, consistent with previous studies.

Sirtuin-1 plays a central role in regulating the cellular stress response as an NAD^+-dependent deacetylase; it exhibits protective effects such as suppression of inflammation, reduction of oxidative stress, and inhibition of apoptosis. Through its NAD^+-dependent deacetylase activity, Sirtuin-1 directly deacetylates pro-inflammatory and pro-apoptotic transcription factors such as NF-κB p65 (RelA) and p53, thereby suppressing their activity and limiting the inflammatory response and cellular death pathways. It has been shown that a decrease in Sirtuin-1 activity under stress conditions is associated with the activation of p53 and NF-κB-mediated proapoptotic and proinflammatory pathways, leading to impaired This study demonstrated that Sirtuin-1 levels decreased significantly during the intraoperative and postoperative periods compared to the preoperative period in patients undergoing cardiac surgery with CPB, and that this suppression occurred simultaneously with an increase in Caspase-3 levels, an executor apoptosis marker. These time-dependent molecular changes reveal that CPB exerts an inhibitory effect on epigenetic-metabolic regulatory mechanisms and is associated with an increased apoptotic response. The findings suggest that the Sirtuin-1–Caspase-3 axis may play an important role in understanding the molecular basis of cellular damage associated with CPB and indicate that Sirtuin-1 could be a potential biomarker and therapeutic target for future protective or modulatory strategies.

Ethics Approval and Consent to Participate

This study was approved by the Harran University Clinical Research Ethics Committee (Decision No: HRÜ/25.18.33; date: 17.11.2025. All procedures were conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. Furthermore, informed consent was obtained from all participants involved in the study.

Data Availability

All data generated or analyzed during this study are included in this published article. The data that support the findings of this study are available on request from the corresponding author, upon reasonable request.

Authors' Contribution

Study Conception: BA; Study Design: BA, ÖG, ME, ŞY; Supervision: BA, ÖG, ME, ŞY; Funding: BA, ÖG; Materials: BA, ÖG; Data Collection and/or Processing: BA, ÖG, ME, ŞY; Statistical Analysis

and/or Data Interpretation: BA, ÖG, ME; Literature Review: BA, ÖG; Manuscript Preparation: BA, ÖG, ME; and Critical Review: BA, ÖG, ME, ŞY.

Conflict of Interest

The author(s) disclosed no conflict of interest during the preparation or publication of this manuscript. Two of the authors of this article (ME, ŞY) are the member of the Editorial Board of this journal. They were completely blinded to the peer review process of the article.

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Generative Artificial Intelligence Statement

The author(s) declare that no artificial intelligence-based tools or applications were used during the preparation process of this manuscript. The all content of the study was produced by the author(s) in accordance with scientific research methods and academic ethical principles.

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