Int J Adv Life Sci Res. Volume 9(2) 186-194
https://doi.org/10.31632/ijalsr.2026.v09i02.014

International Journal of Advancement in Life Sciences Research

Online ISSN: 2581-4877

Journal homepage http://ijalsr.org

Original Article

Oxidative Stress Induced Alterations in Red Blood Cells and Their Role in Cardiovascular Pathophysiology

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Abstract

Introduction: Oxidative stress is a fundamental contributor to cardiovascular pathophysiology, primarily through excessive generation of reactive oxygen species (ROS) that disrupt cellular homeostasis. Red blood cells play a critical role in oxygen transport and redox balance; however, they are highly vulnerable to oxidative damage, which may impair their structural integrity and promote vascular dysfunction. **Objective:** This study aimed to examine oxidative stress-induced alterations in red blood cell parameters, antioxidant defence systems, and inflammatory responses, and to elucidate their potential role in cardiovascular pathophysiology. **Methods:** An experimental laboratory study was conducted using 30 male Wistar rats randomly assigned to control and oxidative stress groups. Oxidative stress was induced by intraperitoneal administration of hydrogen peroxide (H_2O_2) for 14 days. Haematological indices, including red blood cell count, haematocrit, and haemoglobin levels, were evaluated. Oxidative damage and antioxidant status were assessed by measuring malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Serum C-reactive protein (CRP) was analysed as an indicator of systemic inflammation. Data were analysed using independent t-tests with a significance level of α = 0.05. **Results:**The oxidative stress group demonstrated a significant decline in haematological parameters compared with the control group, including red blood cell count (5.98 ± 0.38 vs. 6.75 ± 0.41 ×10⁶/μL, p = 0.001), haematocrit (38.7 ± 3.2% vs. 43.5 ± 2.8%, p = 0.002), and haemoglobin concentration (12.5 ± 1.1 vs. 14.3 ± 0.9 g/dL, p = 0.001). Markers of oxidative damage were markedly elevated, as indicated by increased malondialdehyde levels (5.3 ± 1.0 vs. 2.1 ± 0.6 nmol/mL, p< 0.001). Conversely, antioxidant enzyme activities were significantly reduced in the oxidative stress group, including superoxide dismutase (1.92 ± 0.35 vs. 2.85 ± 0.43 U/mL, p< 0.001), catalase (32.6 ± 4.3 vs. 48.2 ± 5.1 U/mg protein, p< 0.001), and glutathione peroxidase (54.1 ± 7.4 vs. 71.4 ± 6.8 U/mL, p< 0.001). In addition, serum C-reactive protein levels were significantly higher in the oxidative stress group (4.9 ± 1.2 vs. 1.4 ± 0.7 mg/L, p< 0.001), indicating enhanced systemic inflammation. **Conclusion:** Oxidative stress induces pronounced alterations in red blood cell integrity, suppresses antioxidant defence mechanisms, and triggers systemic inflammation. These changes represent key early events in cardiovascular pathophysiology and highlight erythrocyte-related oxidative biomarkers as potential indicators for cardiovascular risk assessment.

Keywords: *Antioxidant Enzymes; Cardiovascular Pathophysiology; Inflammation; Oxidative Stress; Red Blood Cells*

Introduction

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, posing a major burden on global health systems. The development and progression of CVDs are driven by complex and interconnected mechanisms, among which oxidative stress has been widely recognised as a central pathophysiological factor. Oxidative stress occurs when the generation of

Received on : 26th August 2025; Revised version received on :14th January2026; Accepted: 17th March 2026

reactive oxygen species (ROS) exceeds the capacity of endogenous antioxidant defence systems, resulting in oxidative damage to cellular lipids, proteins, and nucleic acids. Persistent oxidative imbalance contributes to endothelial dysfunction, vascular inflammation, and structural remodelling, all of which are hallmarks of cardiovascular pathology (Amponsah-Offeh *et al*., 2023).

Red blood cells (RBCs) play a critical role not only in oxygen transport but also in maintaining redox homeostasis within the circulation. Despite lacking nuclei and mitochondria, erythrocytes are equipped with an efficient antioxidant system, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), which protect them from continuous exposure to oxidative challenges. However, due to their high polyunsaturated fatty acid content and constant contact with oxygen and iron-containing haemoglobin, RBC membranes are particularly vulnerable to oxidative injury (Obeagu *et al*., 2024). Under conditions of excessive oxidative stress, erythrocytes undergo structural and functional alterations, such as increased membrane rigidity, reduced deformability, and enhanced susceptibility to haemolysis. Lipid peroxidation of erythrocyte membranes, commonly reflected by elevated malondialdehyde (MDA) levels, compromises membrane integrity and shortens erythrocyte lifespan. These changes may impair microcirculatory flow and oxygen delivery, thereby exacerbating tissue hypoxia and contributing to cardiovascular dysfunction (Tugasworo *et al*., 2023).

In addition to erythrocyte damage, oxidative stress is closely linked to systemic inflammatory responses. Reactive oxygen species can activate pro-inflammatory signalling pathways, leading to the production of acute-phase proteins such as C-reactive protein (CRP). Elevated CRP levels are strongly associated with endothelial dysfunction, atherosclerotic progression, and increased cardiovascular risk. In addition, elevated C-reactive protein levels confirm the activation of systemic inflammatory responses (Nosalski *et al*., 2024). The interaction between oxidative stress and inflammation creates a self-perpetuating cycle that accelerates cardiovascular disease development (Gwozdzinski *et al*., 2021).

Although extensive evidence supports the role of oxidative stress in cardiovascular diseases, the specific contribution of erythrocyte alterations to cardiovascular pathophysiology remains underexplored. Understanding how oxidative stress affects erythrocyte integrity, antioxidant defence capacity, and inflammatory status may provide valuable insights into early pathophysiological changes preceding overt cardiovascular disease. Therefore, this study aimed to investigate oxidative stress-induced alterations in red blood cell parameters, antioxidant enzyme activity, and inflammatory markers using an experimental rat model to elucidate their potential role in cardiovascular pathophysiology (Kwon *et al*., 2024).

Experimental animal models provide a controlled approach to investigate the biological consequences of oxidative stress and its systemic effects. Hydrogen peroxide (H_2O_2) is commonly used as an oxidative stress inducer due to its ability to diffuse across cell membranes and generate secondary reactive oxygen species. In vivo exposure to H_2O_2 has been shown to mimic oxidative conditions observed in early stages of cardiovascular disorders, making it a relevant model for studying erythrocyte vulnerability, antioxidant depletion, and inflammatory activation under sustained oxidative pressure (Aristoteles *et al*., 2021).

Furthermore, alterations in erythrocyte-related oxidative biomarkers may serve as early indicators of cardiovascular dysfunction before the onset of overt clinical symptoms. Changes in red blood cell indices, lipid peroxidation products, and antioxidant enzyme activities reflect systemic redox imbalance that may precede structural vascular damage. Identifying these early alterations is essential for improving cardiovascular risk stratification and developing preventive strategies. Therefore, elucidating the relationship between oxidative stress–induced erythrocyte alterations and cardiovascular pathophysiology may contribute to the advancement of biomarker-based approaches and antioxidant-targeted interventions in cardiovascular disease management (Wahyu *et al*., 2023).

Material & Methods

This study employed a laboratory-based experimental design to investigate oxidative stress–induced alterations in red blood cells and their potential role in cardiovascular pathophysiology. A total of 30 healthy male Wistar rats (*Rattus norvegicus*), aged 8–10 weeks and weighing 180–220 g, were used as experimental subjects. The animals were housed under standard laboratory conditions with controlled temperature, a 12-hour light–dark cycle, and free access to standard chow and water. Following a one-week acclimatisation period, the rats were randomly assigned into two groups: a control group and an oxidative stress group (Nashrullah *et al*., 2023). All procedures were approved by the Institutional Animal Ethics Committee of IKesT MP No. 000520/KEP IKesT Muhammadiyah Palembang/17 June 2025, and animal care was conducted following established ethical guidelines.

Oxidative stress was induced by intraperitoneal administration of hydrogen peroxide (H_2O_2) for 14 consecutive days at a dose of 1 mmol/kg body weight, which has been reported to be sufficient to generate systemic oxidative imbalance, while the control group received an equivalent volume of physiological saline without an oxidative agent. Throughout the experimental period, the animals were monitored daily for general health status and behavioural changes. At the end of the treatment period, all rats were anaesthetised using a combination of ketamine and xylazine, and blood samples were collected via cardiac puncture under aseptic conditions (Ngadiman *et al*., 2023).

Blood samples were divided into ethylenediaminetetraacetic acid (EDTA) tubes for haematological analysis and plain tubes for serum separation. Red blood cell count, haematocrit, and haemoglobin levels were measured using an automated haematology analyser. Serum was obtained by centrifugation and stored at −80°C until further analysis. Malondialdehyde (MDA) levels, as an indicator of lipid peroxidation, were determined using the thiobarbituric acid-reactive substances (TBARS) method. Antioxidant enzyme activities, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), were measured spectrophotometrically using standardised assay protocols (Pereira *et al*., 2021).

Systemic inflammation was assessed by measuring serum C-reactive protein (CRP) levels using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. All biochemical measurements were performed in duplicate to ensure analytical reliability. Data were expressed as mean ± standard deviation. Statistical analysis was conducted using SPSS software, and comparisons between the control and oxidative stress groups were performed using independent *t*-tests. A *p*-value of less than 0.05 was considered statistically significant (Ghosh & Shcherbik, 2020). All experimental procedures involving animals were approved by the institutional ethics committee and conducted in accordance with established guidelines for the care and use of laboratory animals.

Results

Table 1: *Effects of Oxidative Stress on Hematological, Oxidative, and Inflammatory Parameters*

Parameter	Control Group	Oxidative Stress Group	*p*-value
Red blood cell count (×10⁶/µL)	6.75 ± 0.41	5.98 ± 0.38	0.001
Haematocrit (%)	43.5 ± 2.8	38.7 ± 3.2	0.002
Haemoglobin (g/dL)	14.3 ± 0.9	12.5 ± 1.1	0.001
Malondialdehyde (nmol/mL)	2.1 ± 0.6	5.3 ± 1.0	0.001
Superoxide dismutase (U/mL)	2.85 ± 0.43	1.92 ± 0.35	0.001
Catalase (U/mg protein)	48.2 ± 5.1	32.6 ± 4.3	0.001
Glutathione peroxidase (U/mL)	71.4 ± 6.8	54.1 ± 7.4	0.001
C-reactive protein (mg/L)	1.4 ± 0.7	4.9 ± 1.2	0.001

Values are presented as mean ± standard deviation. Statistical analysis was performed using an independent t-test. A p-value < 0.05 was considered statistically significant

The results presented in Table 1 indicate a comparison of haematological parameters, oxidative stress markers, antioxidant enzyme activities, and inflammatory indicators between the control and oxidative stress groups. Exposure to oxidative stress resulted in a significant reduction in red blood

cell count, haematocrit, and haemoglobin levels, indicating impaired erythrocyte integrity and oxygen-carrying capacity. These haematological alterations were accompanied by a marked increase in malondialdehyde levels, reflecting enhanced lipid peroxidation and oxidative damage to erythrocyte membranes. Concurrently, the activities of key antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, were significantly decreased, suggesting exhaustion of endogenous antioxidant defences. The elevation of C-reactive protein levels further indicates the presence of systemic inflammatory responses. Collectively, these findings demonstrate a close relationship between oxidative stress-induced erythrocyte dysfunction, reduced antioxidant capacity, and inflammation, which may contribute to early cardiovascular pathophysiological changes.

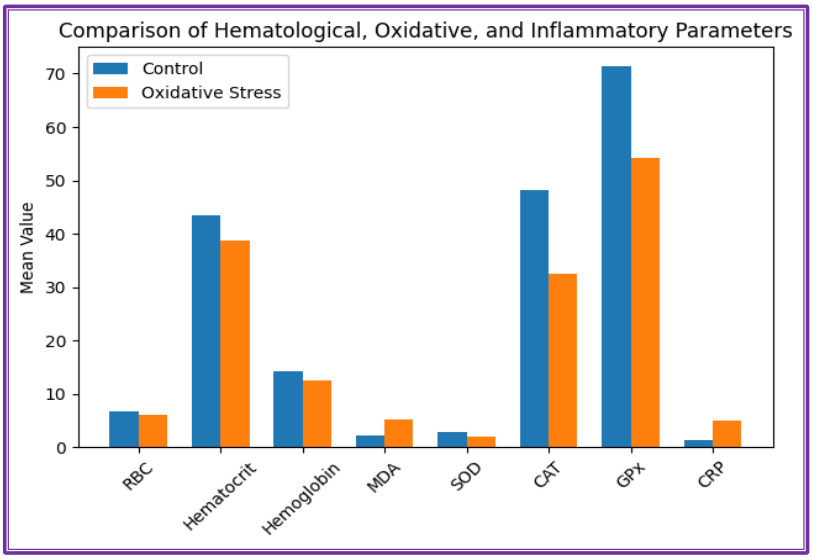

Figure 1: *The Comparative Analysis of Hematological and Biochemical Parameters*

Figure 1 shows the comparison of haematological parameters, oxidative stress markers, antioxidant enzyme activities, and inflammatory status between control and oxidative stress groups. The oxidative stress group shows reduced red blood cell count, haematocrit, haemoglobin, and antioxidant enzyme activities (SOD, CAT, and GPx), accompanied by increased malondialdehyde and C-reactive protein levels, indicating enhanced oxidative damage and systemic inflammation (Tutino *et al*., 2024).

Table 2: *Post Hoc Analysis*

Parameter	**Control Group (Mean ± SD)**	**Oxidative Stress Group (Mean ± SD)**	**Mean Difference**	**95% CI**	***p*-value**	**Effect Size (Cohen's *d*)**
Red blood cell count (×10⁶/μL)	6.75 ± 0.41	5.98 ± 0.38	0.77	0.47 – 1.07	0.001	1.96
Hematocrit (%)	43.5 ± 2.8	38.7 ± 3.2	4.8	2.06 – 7.54	0.002	1.55
Hemoglobin (g/dL)	14.3 ± 0.9	12.5 ± 1.1	1.8	1.00 – 2.60	0.001	1.77
Malondialdehyde (nmol/mL)	2.1 ± 0.6	5.3 ± 1.0	−3.2	−3.84 −2.56	0.001	3.94
Superoxide dismutase (U/mL)	2.85 ± 0.43	1.92 ± 0.35	0.93	0.64 – 1.22	0.001	2.35
Catalase (U/mg protein)	48.2 ± 5.1	32.6 ± 4.3	15.6	12.1 – 19.1	0.001	3.32
Glutathione peroxidase (U/mL)	71.4 ± 6.8	54.1 ± 7.4	17.3	12.3 – 22.3	0.001	2.50
C-reactive protein (mg/L)	1.4 ± 0.7	4.9 ± 1.2	−3.5	−4.15 –2.85	0.001	3.64

Values are presented as mean ± standard deviation. Mean differences were calculated using independent t-test analysis. Effect sizes were estimated using Cohen's d. A p-value < 0.05 was considered statistically significant

The results presented in table II showed post hoc analysis comparing haematological parameters, oxidative stress markers, antioxidant enzyme activities, and inflammatory status between the control and oxidative stress groups. The analysis demonstrates significant differences across all measured variables, with large to very large effect sizes. Oxidative stress was associated with marked reductions in red blood cell count, haematocrit, and haemoglobin, indicating substantial impairment of erythrocyte integrity. These changes were accompanied by a pronounced increase in malondialdehyde levels, reflecting enhanced lipid peroxidation, and significant suppression of antioxidant enzyme activities (SOD, catalase, and glutathione peroxidase). In parallel, C-reactive protein levels were markedly elevated, indicating activation of systemic inflammatory responses. Collectively, the post hoc findings confirm a strong relationship between oxidative stress–induced erythrocyte dysfunction, weakened antioxidant defence, and inflammation, supporting their contributory role in early cardiovascular pathophysiology.

Discussion

This study demonstrates that experimentally induced oxidative stress produces profound alterations in red blood cell integrity, antioxidant defence systems, and inflammatory status, all of which are closely linked to early cardiovascular pathophysiology. The consistent changes observed across haematological parameters, oxidative stress markers, antioxidant enzymes, and inflammatory indicators highlight the central role of oxidative imbalance in disrupting erythrocyte homeostasis and promoting conditions conducive to cardiovascular disease development.

Oxidative Stress and Erythrocyte Dysfunction

The significant reduction in red blood cell count, haematocrit, and haemoglobin observed in the oxidative stress group indicates impaired erythrocyte integrity and oxygen-carrying capacity. Erythrocytes are continuously exposed to high oxygen tension and iron-containing haemoglobin, making them particularly susceptible to oxidative damage. Excessive reactive oxygen species can induce lipid peroxidation of erythrocyte membranes, leading to increased membrane rigidity, reduced deformability, and enhanced susceptibility to haemolysis. These structural alterations shorten erythrocyte lifespan and may disrupt microcirculatory flow, thereby compromising tissue oxygen delivery and exacerbating cardiovascular stress (Wang *et al*., 2023; Awashra *et al*., 2026).

Moreover, oxidative stress may also impair erythropoiesis by damaging erythroid precursors in the bone marrow (El Hoss *et al*. 2026). The combined effects of increased erythrocyte destruction and reduced production may explain the observed decline in haematological indices (Yi *et al*., 2022). Such alterations are clinically relevant, as anaemia and reduced haemoglobin levels are frequently associated with adverse cardiovascular outcomes, including myocardial ischaemia and heart failure (Amponsah-Offeh *et al*., 2023).

Lipid Peroxidation and Redox Imbalance

Malondialdehyde, a well-established end product of lipid peroxidation, was markedly elevated in the oxidative stress group, confirming extensive oxidative damage. Increased MDA levels reflect disruption of erythrocyte membrane lipids and serve as an indicator of systemic oxidative burden. Lipid peroxidation not only alters membrane fluidity and permeability but also generates reactive aldehydes that can further propagate oxidative injury and inflammatory signalling (Alfhili *et al*., 2024). In parallel, the significant reduction in antioxidant enzyme activities, including superoxide dismutase, catalase, and glutathione peroxidase, suggests exhaustion or inactivation of endogenous antioxidant defences under sustained oxidative pressure (Tripathi, 2024).

These enzymes play complementary roles in neutralising reactive oxygen species; therefore, their suppression results in ROS accumulation and amplification of oxidative damage. In erythrocytes, where mitochondrial antioxidant systems are absent, the impairment of these enzymes has particularly detrimental consequences for redox homeostasis (Sadasivam *et al*., 2022).

Inflammation as a Consequence of Oxidative Stress

The marked elevation of C-reactive protein levels in the oxidative stress group indicates activation of systemic inflammatory responses. Oxidative stress is known to stimulate pro-inflammatory signalling pathways, including nuclear factor-kappa B (NF-κB), leading to increased synthesis of acute-phase proteins such as CRP. Elevated CRP not only serves as a biomarker of inflammation but also actively contributes to endothelial dysfunction by promoting leukocyte adhesion, impairing nitric oxide bioavailability, and enhancing a pro-thrombotic state (Kurt *et al*., 2025).

The concurrent presence of oxidative stress and inflammation suggests a bidirectional relationship in which reactive oxygen species trigger inflammatory responses, while inflammation further amplifies oxidative damage (Pereira, 2024). This self-perpetuating cycle accelerates vascular injury and plays a critical role in the initiation and progression of cardiovascular diseases (Aristoteles *et al*., 2024).

Implications for Cardiovascular Pathophysiology

The integrated alterations observed in this study – erythrocyte dysfunction, increased lipid peroxidation, suppressed antioxidant defences, and elevated inflammatory markers – represent

key early events in cardiovascular pathophysiology. Impaired erythrocyte deformability and reduced oxygen delivery may exacerbate myocardial and vascular hypoxia, while oxidative and inflammatory insults promote endothelial dysfunction and atherosclerotic progression (Di Franco *et al*., 2022).

Importantly, the large effect sizes observed in post hoc analyses underscore the biological relevance of these changes. Monitoring erythrocyte-related oxidative and inflammatory biomarkers may therefore provide valuable insights for early cardiovascular risk assessment (dos Santos *et al*., 2020). Furthermore, these findings support the potential therapeutic value of strategies aimed at restoring redox balance, such as antioxidant supplementation or pharmacological enhancement of endogenous antioxidant systems (Valaitienė & Laučytė-Cibulskienė, 2024).

Limitations

Despite its strengths, this study has several limitations. The use of a single oxidative stress inducer may not fully capture the complexity of oxidative mechanisms involved in human cardiovascular disease (Cordiano *et al*., 2023). Additionally, the exclusive use of male animals precludes evaluation of sex-related differences in oxidative stress responses (Krishnamurthy *et al*., 2024).

Future Perspectives

Future studies should incorporate multiple oxidative stimuli, include both sexes, and extend the analysis to vascular and cardiac histopathology to further elucidate the mechanistic links between erythrocyte dysfunction and cardiovascular disease (Abdelazim & Abomughaid, 2024).

Translational Relevance and Clinical Implications

The findings of this study have important translational implications for cardiovascular research and clinical practice. Alterations in erythrocyte-related oxidative and inflammatory biomarkers, such as malondialdehyde, antioxidant enzyme activity, and C-reactive protein, may reflect early systemic changes that precede overt cardiovascular pathology. Because red blood cell parameters are routinely measured in clinical settings, integrating oxidative stress and inflammatory markers into standard haematological assessments could enhance early detection and risk stratification of cardiovascular disease (Gusnirwan & Sangging, 2024).

Furthermore, targeting erythrocyte oxidative damage through antioxidant-based or anti-inflammatory interventions may represent a promising strategy to preserve vascular function and prevent disease progression. These translational insights emphasise the potential role of erythrocytes not only as passive indicators but also as active contributors to cardiovascular pathophysiology (Martínez-Vieyra *et al*., 2025).

Conclusion

This study demonstrates that oxidative stress-induces significant alterations in red blood cell integrity, antioxidant defence systems, and inflammatory status. The observed reductions in red blood cell count, haematocrit, and haemoglobin indicate impaired erythrocyte function, while the marked increase in malondialdehyde levels reflects enhanced lipid peroxidation. Concurrent suppression of key antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, highlights a compromised redox defence system under oxidative conditions.

Collectively, these findings suggest that oxidative stress induced erythrocyte dysfunction, reduced antioxidant capacity, and inflammation are closely interconnected processes that contribute to early cardiovascular pathophysiology. Erythrocyte-related oxidative and inflammatory biomarkers may therefore serve as valuable indicators for cardiovascular risk assessment and represent potential targets for preventive and therapeutic strategies aimed at restoring redox balance and limiting cardiovascular disease progression.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this research.

Acknowledgement

The authors would like to express their sincere gratitude to the Direktorat Jenderal Riset dan Pengembangan, Kementerian Pendidikan Tinggi, Sains dan Teknologi, for the support provided. The authors also thank all research team members for their dedication, hard work, and invaluable collaboration throughout the study. Appreciation is further extended to the laboratory staff and technical assistants for their assistance in sample collection and data analysis for ensuring the smooth operation of the laboratory work. Furthermore, I thank the institution and all administrative staff for their support in facilitating this research project and all participants involved, whose cooperation made this study possible. Without the collective effort of everyone involved, this research would not have been successfully complete.

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