ARYA Atherosclerosis J

Original Article Open Access

Investigation the effects of Rivaroxaban on oxidative stress and antioxidant capacity in patients heart failure

Galia Dilanchian[1], Ziba Rezvani Sichani[1], Hashem Nayeri[1*], Sedigheh Asgary[1,2]

1- Department of Biochemistry, Islamic Azad University, Falavarjan Branch, Isfahan, Iran
2- Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

Correspondence:

Hashem Nayeri;
Department of Biochemistry, Islamic Azad University, Falavarjan Branch, Isfahan, Iran;
Email: hnaieri@gmail.com
hashem.nayeri@iau.ac.ir

Received: 2025-02-02
Accepted: 2025-06-03

How to cite this article:
Dilanchian G, Rezvani Sichani Z, Nayeri H, Asgary S. **Investigation the effects of Rivaroxaban on oxidative stress and antioxidant capacity in patients heart failure.** ARYA Atheroscler. 2025; 21(4): 36-43.

DOI:
https://doi.org/10.48305/arya.2025.43452.3024

Abstract

BACKGROUND: Rivaroxaban, a direct Factor Xa inhibitor, primarily acts by disrupting the coagulation cascade. However, it may also influence oxidative stress. This effect likely stems from its ability to reduce thrombin-mediated reactive oxygen species (ROS) production and mitigate inflammation. The major aim of the present investigation was to assess the effects of Rivaroxaban on oxidative stress and antioxidant capacity in patients with heart failure.

METHODS: This study included 39 patients (17 males and 22 females, aged 30–95 years) with Stage B heart failure (HF) who had never previously received Rivaroxaban. Patients were enrolled from Chamran Cardiovascular Hospital in Isfahan after providing written informed consent, approved by the Falavarjan University Ethical Committee (IR.IAU.FALA.REC.1398.029). All patients had structural cardiac abnormalities, including reduced left ventricular ejection fraction (LVEF < 40%) or diastolic dysfunction, but no clinical symptoms of HF. Rivaroxaban (20 mg/day) was administered orally to all patients for two months using a pre–post design.

Blood samples were collected before and after treatment to assess oxidative stress and antioxidant biomarkers, including total antioxidant capacity (TAC), malondialdehyde (MDA), homocysteine (Hcy), and the enzymatic activities of paraoxonase-1 (PON1) and arylesterase. TAC, MDA, and enzyme activities were measured spectrophotometrically, while homocysteine levels were determined using ELISA.

RESULTS: The results showed a significant reduction in MDA levels ($P < 0.001$), indicating reduced oxidative stress after Rivaroxaban treatment. However, no statistically significant changes were observed in other biomarkers, including homocysteine, arylesterase, paraoxonase, and TAC ($P > 0.05$).

CONCLUSION: In conclusion, Rivaroxaban appears to effectively reduce oxidative stress, as evidenced by decreased MDA levels.

Keywords: Rivaroxaban; Oxidative Stress; Heart Failure; Malondialdehyde; Total Antioxidant Capacity

Introduction

Heart failure (HF) is a complex clinical syndrome characterized by impaired cardiac function, often accompanied by systemic metabolic disturbances, oxidative stress, and inflammation[1]. Stage B HF consists of patients with asymptomatic cardiac structural abnormalities[2]. Oxidative stress, defined as an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defense mechanisms, plays a pivotal role in the pathogenesis and progression of HF[3]. Elevated levels of oxidative stress biomarkers, such as malondialdehyde (MDA), and disrupted antioxidant enzyme activities have been consistently observed in HF patients, contributing to myocardial dysfunction, endothelial injury, and adverse cardiovascular outcomes[4]. Among these biomarkers, MDA serves as a reliable indicator of lipid peroxidation and oxidative damage, while homocysteine a sulfur-containing amino acid—has been implicated in endothelial dysfunction through oxidative stress-mediated pathways[5]. Additionally, paraoxonase-1 (PON1) and arylesterase, enzymes associated with high-density lipoproteins (HDL), play crucial roles in preventing lipid oxidation and maintaining vascular health[6]. Alterations in the activity of these enzymes have been linked to increased cardiovascular risk in HF patients[7].

Anticoagulant therapy, particularly with novel oral anticoagulants (NOACs) such as rivaroxaban, has become a cornerstone in the management of HF patients with comorbid conditions like atrial fibrillation or venous thromboembolism[8]. Beyond its primary role in inhibiting factor Xa and preventing thromboembolic events, rivaroxaban has been hypothesized to exert pleiotropic effects, including potential modulation of oxidative stress and antioxidant defense systems[9].

This medication, when taken in doses ranging from 10 to 20 mg per day, is authorized for several uses, including the treatment and prevention of venous thromboembolism, as well as stroke or systemic embolism prevention in individuals with atrial fibrillation[10]. Previous research has primarily investigated the anticoagulant properties of rivaroxaban and its role in preventing thromboembolic events in patients with HF and atrial fibrillation[11]. Emerging evidence suggests that rivaroxaban may exert effects beyond factor Xa inhibition, potentially influencing oxidative stress and antioxidant defense mechanisms[12].

However, direct and specific data regarding its impact on oxidative stress biomarkers—particularly in patients with Stage B heart failure—remain scarce. Given the pivotal role of oxidative stress in HF pathogenesis, a deeper understanding of these potential effects is warranted[13]. This study aims to address this gap by evaluating the protective effects of rivaroxaban on oxidative stress and cardiovascular outcomes in early-stage HF, a domain that remains relatively underexplored.

In contrast to previous investigations that have primarily examined MDA as a marker of lipid peroxidation[14], we extend our analysis to include key antioxidant enzymes such as PON1 and arylesterase, which have received limited attention in this context. By exploring the molecular mechanisms underlying oxidative stress modulation, the present investigation aims to elucidate the effects of rivaroxaban on oxidative stress and antioxidant capacity in patients with heart failure.

Material and Method

Serum preparation

This clinical study was conducted on patients referred to Chamran Cardiovascular Hospital in Isfahan, after obtaining written informed consent, which was approved by the Falavarjan University Ethical Committee (IR.IAU.FALA.REC.1398.029). The participants had structural cardiac abnormalities, such as reduced left ventricular ejection fraction (LVEF < 40%) or diastolic dysfunction, but showed no clinical symptoms of heart failure (HF) and were classified as Stage B HF. The study included 39 patients (17 males and 22 females), aged 30–95 years, with the sample size determined based on previous studies in similar populations and patient recruitment feasibility[15].

Patients with heart failure and atrial fibrillation who had never previously received Rivaroxaban were included in the study, and individuals with mitral valve stenosis, prosthetic heart valves, a history of acute stroke in the past six months, acute liver disease, conditions predisposing them to bleeding, creatinine clearance below 30 mL/min, or pregnancy were excluded.

Rivaroxaban (20 mg/day) was then administered orally to all patients for 2 months. It is noteworthy that the patients were receiving Rivaroxaban for the first time and were not using any other medication. Blood samples were collected from the patients at two time points: first, before starting treatment with Rivaroxaban, and second, 2 months after taking 20 mg of Rivaroxaban daily. Serum separation was performed via centrifugation at 3,000 rpm for 10 minutes. The separated serum was transferred to microtubes and stored at −70°C in the freezer at the Isfahan Cardiovascular Research Center, Isfahan, Iran. The levels of biochemical parameters, including MDA, PON1, Hcy, and TAC, were measured.

An echocardiogram was performed on all patients; the ejection fraction was determined using the modified Simpson method. Left ventricular systolic function was considered preserved if the ejection fraction was ≥45%[16].

Biochemical Analysis

Measurement of TAC

The total antioxidant capacity was measured using the ABTS assay. In this method, ABTS (2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)) is oxidized to form a blue-green $ABTS^+$ radical. The antioxidants in the sample reduce the $ABTS^+$ radical back to the colorless ABTS form. The level of antioxidants in the sample is determined by measuring the decrease in absorbance at 420 nm using a spectrophotometer. This decrease in absorbance is directly proportional to the antioxidant capacity of the sample[17].

Measurement of MAD

The lipid peroxidation assessment kit (Malondialdehyde concentration) was obtained from Tali Gene Pars Company. The assessment of lipid peroxidation (Malondialdehyde) was performed manually using the spectrophotometric method. In this method, Malondialdehyde present in the sample reacts with thiobarbituric acid (TBA) at a high temperature (95°C), forming the MDA-TBA compound. The resulting MDA-TBA compounds were monitored using colorimetry at a wavelength of 523 nanometers[18].

Measurement of Hcy

Homocysteine levels were measured using an enzyme-linked immunosorbent assay (ELISA) method. The Axis Homocysteine EIA Kit (Axis-Shield Diagnostics Ltd., Scotland, UK) was used for this assay. In this method, 25 µL of plasma is mixed with specific reagents that bind homocysteine. The amount of bound homocysteine is then determined by measuring the absorbance at 405 nm using a spectrophotometer or plate reader. The higher the absorbance, the greater the concentration of homocysteine in the plasma sample[19].

Measurement of PON1 Enzyme Activity

The activity of paraoxonase (an organophosphate hydrolase) was determined using the Beltowski method, which involves measuring the initial rate of hydrolysis of paraoxon to produce paranitrophenol (p-nitrophenol). For this assay, a buffer solution was prepared containing 100 mM Tris-HCl, 2 mM $CaCl_2$, and 2 mM paraoxon at pH 8. To initiate the reaction, 10 µL of the enzyme was added to the assay mixture, resulting in a final volume of 520 µL. The rate of p-nitrophenol production was monitored spectrophotometrically at a wavelength of 412 nm[20].

Measurement of Aryl esterase activity

The arylesterase activity of PON1 was assessed by measuring the initial rate of phenyl acetate hydrolysis. According to the Beltowski method, an assay solution was prepared using a buffer containing 100 mM Tris-HCl, 2 mM $CaCl_2$, and 2 mM phenyl acetate at pH 8. To initiate the reaction, 10 µL of the enzyme solution was

added, bringing the final volume to 520 µL. The production of phenol, resulting from the hydrolysis of phenyl acetate, was monitored spectrophotometrically at a wavelength of 270 nm. Arylesterase activity was calculated using equations (1) and (2), with the micromolar extinction coefficient set to 0.001310[20].

Statistical Analysis

All collected data were entered into SPSS software, version 20. The normal distribution of continuous variables was assessed using the Shapiro–Wilk test. Based on the results, most variables followed a normal distribution; therefore, parametric tests were applied. Descriptive statistics were expressed as mean ± standard deviation (SD). To compare pre- and post-intervention values, the paired t-test was used. Pearson correlation coefficients were calculated to evaluate relationships between different biochemical variables. A p-value of less than 0.05 was considered statistically significant.

Result

Biochemical parameters

According to Table 1, Rivaroxaban demonstrated a positive effect by reducing the malondialdehyde concentration from an average of 13.60 to 7.43 ($P < 0.001$). However, based on the results obtained from this study, it is important to note that Rivaroxaban use in cardiac patients did not have a significant positive impact on other cardiovascular risk factors. Nevertheless, a significant correlation was observed between paraoxonase enzyme activity and total antioxidant capacity, indicating that an increase in paraoxonase activity is associated with an increase in total antioxidant capacity.

Correlation Among Measured Factors Before and After the Intervention

The results in Table 2 indicate that, among the measured factors before the intervention, there was no significant linear relationship between variables, as the significance levels in all cases exceeded the 5% error threshold ($P > 0.05$). Among the factors measured after the intervention, only the relationship between total antioxidant capacity and paraoxonase activity was statistically significant ($P < 0.05$).

Discussion

This study aimed to evaluate the effect of Rivaroxaban on oxidative stress markers and enzymatic activity related to antioxidant defense in cardiac patients. The results indicated that, while Rivaroxaban significantly reduced MDA levels, it did not have a notable impact on other critical cardiovascular risk factors, including TAC, Hcy, PON1, and arylesterase activities. These findings suggest a selective effect of Rivaroxaban on oxidative stress[21].

The significant reduction in malondialdehyde (MDA) following treatment with Rivaroxaban is a pivotal finding. According to previous studies, MDA recognized as a primary marker of oxidative stress is directly associated with cellular damage and the progression of cardiovascular diseases, particularly heart failure[22]. In heart failure patients, elevated MDA levels may indicate severe damage to cardiac tissues and endothelial dysfunction, which contribute to disease progression and the development of further complications[23].

Table 1. Comparison of biochemical parameters between before and after intervention

Variables	Before Intervention (N=39)	After Intervention (N=39)	Change%	P-Value
	Mean±SD	Mean±SD		
Hcy µmol/L	13.8±6.88	13.27±5.07	4.3	0.454
ARE U/L	124.76±24.56	126.74±26.00	1.5	0.802
PON1 U/L	52.13±33.19	52.73±30.93	1.15	0.752
MDA µmol/L	13.60±7.47	7.43±3.49	45	0.001*
TAC µmol/L	2.97±1.61	2.46±1.29	17	0.374

HCy;Homocysteine , ARE;Aryl esterase, PON1;Paraoxonase, MDA;Malondialdehyde, TAC;Total Antioxidant Capacity, *,P value of department T-test, Change%; percentage change in each biochemical parameter between before and after the intervention.

Table 2. Correlation Among Measured Factors Before and After the Intervention

Variables Compared	Pearson correlation	P-value
Hcy (µmol/L) & ARE (U/L) (Before)	0.125	0.588
Hcy (µmol/L) & ARE (U/L) (After)	0.187	0.429
Hcy (µmol/L) & PON1(U/L) (Before)	0.090	0.699
Hcy (µmol/L) & PON1(U/L) (After)	0.274	0.243
Hcy (µmol/L) & MDA(µmol/L) (Before)	-0.144	0.533
Hcy (µmol/L) & MDA(µmol/L) (After)	-0.002	0.994
Hcy (µmol/L) & TAC(µmol/L) (Before)	0.423	0.056
Hcy (µmol/L) & TAC (µmol/L) (After)	-0.002	0.077
ARE (U/L)& PON1 (U/L) (Before)	-0.169	0.464
ARE (U/L)& PON1 (U/L) (After)	0.134	0.574
ARE (U/L)& MDA(µmol/L) (Before)	-0.169	0.463
ARE(U/L) & MDA (µmol/L) (After)	-0.177	0.455
ARE (U/L)& TAC (µmol/L) (Before)	-0.268	0.240
ARE (U/L)& TAC (µmol/L) (After)	-0.177	0.811
PON1 (U/L)& MDA (µmol/L) (Before)	-0.208	0.365
PON1 (U/L)& MDA (µmol/L) (After)	-0.099	0.678
PON1 (U/L)& TAC (µmol/L) (Before)	-0.035	0.879
PON1 (U/L)& TAC (µmol/L) (After)	-0.099	0.037 ★
MDA (µmol/L)& TAC (µmol/L) (Before)	-0.099	0.678
MDA (µmol/L)& TAC (µmol/L) (After)	-0.099	0.972

★ Statistically significant at $P < 0.05$,Hcy: Homocysteine, PON1: Paraoxonase-1, TAC: Total Antioxidant Capacity, MDA: Malondialdehyde, ARE ;Aryl esterase.

Studies have shown that Rivaroxaban, as a direct Factor Xa inhibitor, reduces thrombin production and subsequently lowers reactive oxygen species (ROS) levels, leading to decreased lipid peroxidation and, consequently, reduced MDA production an outcome that aligns with the findings of this study. Moreover, the reduction in oxidative stress is often accompanied by improved endothelial function, which is essential for controlling blood pressure and preventing new cardiovascular events[24]. Therefore, the decline in MDA levels may not only mitigate oxidative stress but also potentially improve clinical outcomes for heart failure patients[25].

One notable observation from this study is the significant positive correlation between paraoxonase activity and total antioxidant capacity (P = 0.037, r = 0.468), indicating that increased paraoxonase activity is associated with greater overall antioxidant capacity. Paraoxonase, an HDL-associated enzyme, plays a crucial role in preventing LDL oxidation and is considered a key component of the body's antioxidant defense system[26]. The observed correlation highlights the potential role of PON1 in modulating antioxidant defenses in cardiac patients[27].

Despite the absence of a direct effect of Rivaroxaban on paraoxonase activity, its significant association with TAC suggests that paraoxonase may act as a mediator of antioxidant status in this population[28]. These results are consistent with prior studies reporting that increased PON1 activity is linked with enhanced

antioxidant capacity and reduced cardiovascular risk[29]. Furthermore, the observed correlation between TAC and PON1 in this study may indicate a synergistic relationship between antioxidant and detoxification functions, potentially contributing to reduced oxidative damage and improved cardiac performance.

This finding aligns with multiple prior investigations. Previous research has demonstrated that PON1, as an antioxidant enzyme, can influence and enhance the body's total antioxidant capacity. For instance, one study reported that elevated PON1 activity correlated with higher TAC, and both biomarkers were jointly involved in reducing oxidative stress and cardiovascular damage[30].

The absence of a significant correlation between homocysteine levels and antioxidant enzymes such as PON1 and arylesterase suggests that Rivaroxaban may not influence homocysteine metabolism a well-known risk factor for cardiovascular disease[29]. This outcome contrasts with studies reporting a relationship between hyperhomocysteinemia and reduced paraoxonase activity, which contributes to impaired HDL function and elevated cardiovascular risk[31]. The lack of a significant effect in this study may be attributed to the short treatment duration, differences in patient populations, or the specific mechanisms of action of Rivaroxaban compared to other interventions targeting homocysteine metabolism.

Conclusion

While Rivaroxaban demonstrates a beneficial effect in reducing MDA levels, its limited impact on other oxidative stress markers suggests that it may not provide comprehensive antioxidant protection in cardiac patients. Further research is needed to explore strategies that can enhance overall antioxidant status and more effectively reduce cardiovascular risk.

Potential Limitations

his study was conducted at a single center, Chamran Cardiovascular Hospital, which may limit the generalizability of the results to a broader population. Multicenter studies involving more diverse patient populations could yield more widely applicable conclusions. Additionally, while this study focused on a range of oxidative stress markers (MDA, PON1, Hcy, TAC), the inclusion of additional biomarkers related to inflammation, endothelial dysfunction, or cardiac injury could provide a more comprehensive understanding of Rivaroxaban's effects on heart failure. The absence of a control group (patients not receiving Rivaroxaban) makes it difficult to attribute observed changes directly to the treatment. Future studies incorporating control groups are recommended to confirm the specific effects of Rivaroxaban on oxidative stress biomarkers.

Acknowledgements

The authors would like to thank Isfahan Cardiovascular Research Center and Chamran Cardiovascular Hospital.

Conflict of interests

The authors declare no conflict of interest.

Funding

There is no funding in this study.

Author's Contributions

Study Conception or Design: GD; HN
Data Acquisition: GD; SA
Data Analysis or Interpretation: GD; ZRS
Manuscript Drafting: GD; ZRS; HN; SA
Critical Manuscript Revision: GD; ZRS; HN; SA
All authors have approved the final manuscript and are responsible for all aspects of the work.

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