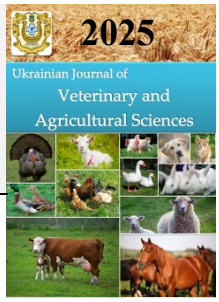
Ukrainian Journal of
Veterinary and Agricultural Sciences
http://ujvas.com.ua

The Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologies Lviv

original article | UDC 616.12-092:615.273.4 | doi: 10.32718/ujvas8-1.10

Volume 8
Number 1



Cardioprotective effects of L-arginine in a mesatone-induced rat model of chronic heart failure: biochemical and electrocardiographic insights

R. V. Mylostyvyi[1], M. O. Lieshchova[1], P. M. Skliarov[1], N. I. Suslova[1], O. V. Yanovska[1], Iu. A. Gordiienko[1], O. V. Khmelova[1], V. V. Vakulik[1], B. V. Gutyj[2]

[1]*Dnipro State Agrarian and Economic University, S. Efremov Str., 25, 49600, Dnipro, Ukraine*
[2]*Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologies Lviv, Pekarska Str., 50, Lviv, 79010, Ukraine*

Article info
Received 14.01.2025
Received in revised form 17.02.2025
Accepted 18.02.2025

Correspondence author
Roman Mylostyvyi
Tel.: +38-097-280-88-19
E-mail: mylostyvyi.r.v@dsau.dp.ua

Abstract

The management of chronic heart failure (CHF) remains a critical challenge in cardiovascular pathology. This study aimed to investigate the role of L-arginine in a mesatone-induced rat model of CHF. L-arginine exhibits cardioprotective effects. CHF was induced in experimental groups by intramuscular administration of 0.1 mL of a 1 % mesatone solution, followed by daily free swimming until profound fatigue for 21 days. The experiment continued until stable and irreversible myocardial changes developed. One experimental group received L-arginine at a dose of 20 mg/kg intraperitoneally for 10 days. The control group consisted of intact animals. The impact of CHF on the cardiovascular system was assessed through biochemical and electrocardiographic (ECG) parameters. In CHF-induced rats, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels increased by 36.7 % ($P \leq 0.05$) and 184.1 % ($P \leq 0.05$), respectively, compared to the control group. Additionally, CHF was associated with an increase in creatinine levels by 152.6 % ($P \leq 0.01$) and urea levels by 207.0 % ($P \leq 0.05$), indicating renal dysfunction. Electrolyte imbalances included elevated sodium, potassium, and chloride levels, reflecting the activation of the renin-angiotensin-aldosterone system (RAAS). CHF also caused significant alterations in ECG parameters, including a 24.8 % ($P \leq 0.05$) reduction in heart rate, a 50.2 % ($P \leq 0.05$) decrease in R-wave amplitude, and a 192.9 % ($P \leq 0.05$) reduction in T-wave amplitude. Additionally, CHF led to a 37.2 % ($P \leq 0.05$) prolongation of the QRS complex and a 60.3 % ($P \leq 0.05$) increase in QT interval duration, indicating myocardial conduction abnormalities and impaired ventricular repolarization. L-arginine administration demonstrated a cardioprotective effect by reducing AST levels by 27.7 % ($P \leq 0.05$) and ALT by 5.8 %, suggesting improved myocardial function. Furthermore, creatinine and urea levels decreased by 46.9 % ($P \leq 0.05$) and 60.0 % ($P \leq 0.05$), respectively, indicating a beneficial effect on renal function. Electrolyte imbalances were partially corrected, with potassium levels decreasing by 69.9 % ($P \leq 0.05$) and chloride levels by 44.1 % ($P \leq 0.05$). L-arginine also contributed to the partial normalization of ECG parameters, leading to a 9.0 % ($P \leq 0.05$) increase in heart rate, reduction in QT interval prolongation, and improved ventricular conduction. These findings suggest that L-arginine mitigates biochemical and electrophysiological disturbances associated with CHF, supporting its potential as a cardioprotective agent.

Keywords: chronic heart failure; mesatone model; biochemical markers; L-arginine; dietary supplement; cardioprotection; electrolytes; electrocardiography.

Citation:
Mylostyvyi, R. V., Lieshchova, M. O., Skliarov, P. M., Suslova, N. I., Yanovska, O. V., Gordiienko, Iu. A., Khmelova, O. V., Vakulik, V. V., & Gutyj, B. V. (2025). Cardioprotective effects of L-arginine in a mesatone-induced rat model of chronic heart failure: biochemical and electrocardiographic insights. *Ukrainian Journal of Veterinary and Agricultural Sciences*, 8(1), 70–76.

1. Introduction

Heart failure remains a growing global epidemic, with an estimated prevalence exceeding 37.7 million individuals worldwide. It is not a distinct disease or diagnosis but rather a syndrome in which severe dysfunction leads to the inability of the cardiovascular system to maintain adequate circulation (Greene et al., 2023). However, diagnosing this pathological condition is often challenging, as some clinical signs are not organ-specific, and the disease may present with minimal symptoms in its early stages. In cardiac disorders such as dilated cardiomyopathy or mitral valve endocardiosis, the body activates compensatory mechanisms to normalize cardiac function and mitigate the negative effects of the disease. These mechanisms enable compensation for mild, moderate, and even severe cardiac dysfunction, often over several years. However, progressive myocardial changes and prolonged activation of compensatory responses ultimately result in cardiac damage, systemic organ dysfunction, and heart failure (Ziaeian & Fonarow, 2016).

Clinically, heart failure is classified as either acute (e.g., acute decompensated congestive heart failure, hypertensive

crisis-related heart failure, pulmonary oedema, cardiogenic shock, high-output heart failure, right ventricular failure) or chronic (categorized by functional classes I, II, III, and IV) and by clinical stages I, II, and III. Chronic heart failure (CHF) is a complex, polyetiological clinical syndrome characterized by a primary reduction in cardiac pump function, which triggers intricate compensatory and pathological hemodynamic, neurohormonal, and metabolic disturbances. Clinically, CHF manifests as dyspnea, palpitations, fatigue, reduced exercise tolerance, and signs of fluid retention (Huang et al., 2021).

CHF symptoms and severity vary widely, ranging from mild exercise intolerance and increased fatigue to dyspnea with minimal exertion, tachypnea, tachycardia, pulmonary rales, cardiomegaly, ventricular gallop sounds, and peripheral oedema. In most cases, CHF and circulatory failure result from a complex interplay between pump dysfunction and changes in peripheral circulation (Schwinger, 2021). CHF reflects the progression of underlying myocardial dysfunction (ischemia, cardiomyopathy, valvular abnormalities, etc.), neurohormonal adaptations, and their subsequent effects on the heart and systemic circulation (Otsuka et al., 2023).

The decline in cardiac output following myocardial injury initiates a cascade of hemodynamic and neurohormonal disturbances, leading to activation of the neuroendocrine system, particularly the adrenergic system and the renin-angiotensin-aldosterone system (RAAS). In diastolic heart failure (heart failure with preserved ejection fraction), the same pathophysiological processes that reduce cardiac output in systolic failure occur, but in response to a distinct set of hemodynamic and circulatory factors (Hartupee & Mann, 2017).

CHF is associated with electrolyte imbalances, including hyponatremia and hyperkalaemia, and leukocytosis in the decompensated stage. Approximately one-third of heart failure patients exhibit iron deficiency, which impairs cardiomyocyte contraction by disrupting mitochondrial respiration, reducing contractility and myocardial relaxation (Arvanitaki et al., 2020). Elevated urea and creatinine levels in CHF are linked to renal dysfunction, while increased alanine aminotransferase (ALT) levels indicate hepatic impairment (Zhou et al., 2024).

Electrocardiographic (ECG) changes resulting from electrolyte imbalances reflect alterations in cardiac transmembrane potentials. When interpreting these abnormalities, it is essential to consider the combined effects of baseline ECG changes, non-specific heart rate fluctuations, arrhythmias, and conduction disturbances.

Modelling pathological conditions in laboratory animals is a fundamental approach in biomedical research, allowing for a controlled investigation of disease mechanisms and potential therapeutic interventions (Lieshchova et al., 2023; Verveha et al., 2023). Experimental models of cardiovascular diseases, including chronic heart failure (CHF), enable the simulation of pathological processes observed in clinical practice, facilitating the evaluation of new treatment strategies. The use of standardized models ensures reproducibility and enhances the translational value of findings, bridging the gap between preclinical research and clinical applications (Antonenko et al., 2020; Lieshchova et al., 2022).

L-arginine is a conditionally essential amino acid that serves as a precursor for the biosynthesis of various biologically active compounds, including nitric oxide, agmatine, creatine, urea, proteins, and polyamines. It plays a crucial role in cell growth, differentiation, repair, immune response, inflammation, and vascular tone regulation (Bahls et al., 2018). The biological role of L-arginine in cardiovascular physiology and pathophysiology has been extensively studied over the past decades, primarily due to its involvement in the biosynthesis of endogenous antioxidants and nitric oxide (Suzuki, 2019; Hsu & Tain, 2020). Nitric oxide is a key regulator of fibrinolysis, haemostasis, vascular tone, endothelial function, and apoptosis in various tissues. Both preclinical and clinical studies have demonstrated an association between circulating L-arginine deficiency and cardiovascular risk (Acevedo et al., 2017). These findings have expanded research efforts into the potential application of L-arginine in cardiovascular diseases.

2. Materials and methods

Experimental model of chronic heart failure

The experimental modelling of chronic heart failure (CHF) in rats was performed using the mesaton-induced CHF model. Mesaton (phenylephrine), an α-adrenergic agonist, was selected for this model due to its potent stimulatory effect on α-adrenergic receptors. Activation of α1-receptors leads to increased myocardial contractility, systemic vasoconstriction, elevated total peripheral vascular resistance and arterial pressure, as well as an increase in venous tone. This results in greater venous return to the heart, subsequently increasing both preload and afterload. Compared to norepinephrine and epinephrine, mesaton induces a less abrupt rise in blood pressure but has a longer duration of action.

The study was conducted on male Wistar rats (n = 22), aged six months, with a body weight of 245–250 g. The animals were housed under standard vivarium conditions in accordance with international guidelines for laboratory animal care. They were provided with a balanced diet and had unrestricted access to water. The experimental protocol adhered to the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (European Convention, 1986) and was approved by the Bioethics Commission of Dnipro State Agrarian and Economic University.

Three groups of animals were formed (n = 30). The control group consisted of healthy animals (n = 8). CHF was induced in the remaining rats, after which they were divided into two experimental groups: Group 1 (n = 11) consisted of animals with untreated CHF, while Group 2 (n = 11) received L-arginine at a dose of 20 mg/kg intraperitoneally for 10 days.

CHF induction protocol

The CHF model was induced according to the following protocol: experimental animals received an intramuscular injection of 0.1 mL of a 1 % mesaton solution, followed by free swimming to the point of profound fatigue. The swimming sessions lasted an average of 25–30 minutes per day for 21 consecutive days. The duration of the experiment was chosen to ensure the development of stable and irreversible cardiac changes.

Biochemical blood analysis

Laboratory analyses were performed using biochemical blood tests. Blood sample collection was conducted following standard protocols. A total of 1.5 mL of blood was drawn from the lateral tail vein of each rat using an intravenous catheter and collected into plastic tubes. Serum was obtained by centrifugation at 3,000 rpm for 15 minutes. The concentrations of biochemical parameters in the collected serum were determined using spectrophotometric analysis with the Miura-200 automatic biochemical analyzer (Italy). The selected biochemical markers included indicators of cardiac function, such as urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), sodium, calcium, potassium, magnesium, and chloride.

Electrocardiographic examination

Electrocardiography (ECG) was performed using a single-channel MEDINOVA ECG-9801 electrocardiograph. The ECG was printed on 50-mm thermal paper in automatic mode using lead I, with a calibration signal of 20 mV and a recording speed of 25 mm/s.

Statistical analysis

Statistical data processing was conducted using Statistica 12 software, applying non-parametric analysis methods, specifically the Mann–Whitney U test. Differences were considered statistically significant at $P \leq 0.05$.

3. Results and discussion

3.1 Results

The mesatone-induced model of chronic heart failure (CHF) in rats led to stable structural and functional alterations in the myocardium. The final symptom complex included a weak apical impulse on palpation, a soft systolic murmur, and a gallop rhythm upon auscultation. Additionally, an increase in capillary refill time to 3.5–4 seconds and a reduction in body temperature were observed. The progression of the induced pathology in most rats (n = 18) was accompanied by worsening dyspnea, with auscultation of the lungs revealing harsh breathing, prolonged expiration, and wheezing sounds. Affected rats exhibited an open-mouth breathing pattern, and cyanosis of the skin and mucous membranes was evident. These clinical signs indicated the development of CHF.

At autopsy, thickened left ventricular walls filled with blood were noted. The thickened myocardial fibers prominently protruded compared to the other two cardiac layers, and delayed vascular and neural fiber development was evident relative to the muscular tissue. The cardiac chambers were reduced in volume, corresponding to left-sided CHF caused by mitral valve insufficiency.

In a subset of rats (n = 4), a uniform increase in abdominal cavity volume and taut skin over the abdomen was observed, indicative of fluid accumulation (ascites). These animals also exhibited progressive weight gain. Ascites was confirmed by abdominal paracentesis, which allowed for fluid aspiration. The formation of ascitic fluid in these rats was associated with blood congestion in the abdominal cavity due to impaired venous return resulting from myocardial insufficiency.

Upon post-mortem examination, these rats displayed enlarged cardiac chambers with thinning of the myocardial walls. Thus, the mesatone-induced CHF model resulted in left-sided CHF in 81.2 % of cases and right-sided CHF in 18.8 % of cases. Body weight in rats with left-sided CHF decreased by 22.4 %, whereas in those with right-sided CHF, it decreased by 16.5 % ($P \leq 0.05$) (Table 1). This difference is attributed to the accumulation of ascitic fluid in rats with right-sided CHF, which contributed to an overall increase in body mass.

Table 1

Changes in heart parameters in rats with CHF

Index	Experimental conditions		
	Control (n = 8)	Rats with left-sided CHF (n = 18)	Rats with right-sided CHF (n = 4)
Body weight, g	232.13 ± 4.07	189.6 ± 10.53*	199.2 ± 8.24
Heart weight, mg	960.1 ± 74.33	1245.3 ± 97.18*	1088.2 ± 29.33
MMI (heart weight, mg/body weight, g)	4.02 ± 0.45	7.13 ± 0.44*	5.65 ± 0.66*
Heart volume, cm^3	1.01 ± 0.035	1.35 ± 0.056	1.69 ± 0.04*

Notes: MMI – myocardial mass index. In this and subsequent tables: *$P \leq 0.05$ – significance compared to the control group (Mann-Whitney U test)

The heart mass in both CHF groups exceeded that of the control rats by 29.7 % ($P \leq 0.05$) in left-sided CHF and by 13.3 % in right-sided CHF. The myocardial mass index (MMI) was significantly elevated in CHF-affected rats, with an increase of 77.4 % ($P \leq 0.05$) in left-sided CHF and 40.5 % ($P \leq 0.05$) in right-sided CHF compared to the control group. These findings indicate that left-sided CHF led to significant myocardial hypertrophy without a corresponding increase in heart size, whereas right-sided CHF was characterized by myocardial thinning. Despite myocardial atrophy, the heart mass remained elevated in right-sided CHF due to fibrotic replacement of myocardial tissue.

Heart volume increased by 33.7 % in left-sided CHF and by 67.3 % ($P \leq 0.05$) in right-sided CHF. Despite the greater heart mass in left-sided CHF, cardiac enlargement was more pronounced in right-sided CHF, reflecting differing pathological mechanisms in these conditions.

Biochemical changes in CHF and the effects of L-arginine

Significant differences were observed in the blood parameters of healthy rats, CHF-induced rats, and CHF-induced rats treated with L-arginine (Table 2). In CHF-induced rats, aspartate aminotransferase (AST) activity increased by 184.1 %, whereas alanine aminotransferase (ALT) levels rose by only 36.7 % ($P \leq 0.05$) compared to the control group.

Table 2
Changes in biochemical blood composition in CHF-induced rats and after L-arginine administration

Index	Experimental conditions		
	Control group	CHF model	CHF + L-arginine
Urea, mmol/L	5.74 ± 0.42	17.62 ± 1.54*	11.03 ± 1.66
Creatinine, mmol/L	64.22 ± 0.91	162.25 ± 4.25*	110.48 ± 0.14*
AST, U/L	135.2 ± 3.66	384.1 ± 8.27*	301.82 ± 7.63*
ALT, U/L	127.0 ± 3.79	173.6 ± 3.37*	164.04 ± 1.83
LDH, U/L	210.0 ± 3.77	304.0 ± 8.34*	262.3 ± 9.16
CPK, U/L	144.3 ± 12.41	201.3 ± 19.43	184.4 ± 24.92
Sodium, mmol/L	100.60 ± 9.84	125.60 ± 2.85*	134.0 ± 4.66
Potassium, mmol/L	4.21 ± 0.24	7.22 ± 1.22*	4.25 ± 0.783*
Calcium, mmol/L	2.57 ± 0.11	2.64 ± 0.41	2.70 ± 0.27
Magnesium, mmol/L	2.09 ± 0.23	2.18 ± 0.25	2.12 ± 0.34
Chloride, mmol/L	82.33 ± 1.29	123.14 ± 1.46*	118.61 ± 4.46

Note: AST – aspartate aminotransferase, ALT – alanine aminotransferase, LDH – lactate dehydrogenase, CPK – creatine phosphokinase

L-arginine administration resulted in a 27.7 % ($P \leq 0.05$) decrease in AST levels and a 5.8% reduction in ALT levels in CHF-induced rats. LDH activity in CHF rats increased by 44.7 % ($P \leq 0.05$), while L-arginine treatment led to a 15.9 % reduction. Creatine phosphokinase (CPK) activity was 39.5 % ($P \leq 0.05$) higher in CHF rats, indicating possible myocardial infarction in some individuals. L-arginine administration reduced CPK levels by 27.8 %.

A 152.6 % ($P \leq 0.01$) increase in creatinine and a 207.0 % ($P \leq 0.05$) rise in urea in the CHF model suggest the development of cardiorenal syndrome. Following L-arginine administration, creatinine levels declined by 46.9 % ($P \leq 0.05$) and urea by 60.0 % ($P \leq 0.05$), indicating renal function improvement. These findings suggest that L-arginine may be beneficial in managing both cardiorenal syndrome and primary renal pathology.

Elevated sodium (24.9 %, $P \leq 0.05$), potassium (71.5 %, $P \leq 0.05$), and chloride (49.6 %, $P \leq 0.05$) levels in CHF rats were attributed to renin-angiotensin-aldosterone system activation. L-arginine administration reduced potassium by 69.9 % ($P \leq 0.05$) and chloride by 44.1 %. No significant changes were observed in calcium or magnesium levels.

These biochemical findings indicate significant impairment of cardiac and renal function in CHF-induced rats, while L-arginine treatment showed a positive trend in correcting these pathological changes.

Electrocardiographic changes in CHF and the effects of L-Arginine

To confirm the biochemical findings, electrocardiographic (ECG) analysis was performed on healthy rats, CHF-induced rats, and CHF-induced rats treated with L-arginine (Table 3). A significant reduction in heart rate (HR) by 24.8 % ($P \leq 0.05$) was observed in CHF-induced rats. However, L-arginine administration resulted in a 9.0 % ($P \leq 0.05$) increase in HR.

Table 3
ECG changes in CHF-induced rats and the effects of L-arginine

Index	Experimental conditions		
	Control group	CHF model	CHF + L-arginine
Heart rate, bpm	387 ± 13.07	310 ± 25.15	422 ± 17.16*
P wave duration, s	0.031 ± 0.006	0.033 ± 0.019	0.029 ± 0.015
P wave amplitude, mV	0.132 ± 0.028	0.12 ± 0.087	0.034 ± 0.007*
P-R interval, s	0.058 ± 0.009	0.068 ± 0.007*	0.061 ± 0.011*
QRS duration, s	0.043 ± 0.007	0.059 ± 0.009*	0.05 ± 0.009
Q wave amplitude, mV	0.00 ± 0.000	0.106 ± 0.039*	0.027 ± 0.007
R wave amplitude, mV	1.083 ± 0.24	0.721 ± 0.05*	0.232 ± 0.02*
S wave amplitude, mV	0.165 ± 0.024	0.332 ± 0.057	0.044 ± 0.026*
QT interval, s	0.078 ± 0.017	0.125 ± 0.031*	0.096 ± 0.0114*
T wave amplitude, mV	0.082 ± 0.044	0.028 ± 0.007	0.035 ± 0.006

In 18 % of cases, rats exhibited atrial fibrillation. Following L-arginine administration, a regular rhythm was restored in only 50 % of affected rats. HR in rats with atrial fibrillation ranged from 375 to 571 bpm.

In normal rats, the ECG profile has characteristic features, including the absence of a Q wave. Consequently, instead of measuring the P-Q interval, the P-R interval was assessed. However, in 73 % of CHF-induced rats, the presence of a Q wave was recorded, suggesting the development of dilated cardiomyopathy and mitral valve endocardiosis. The persistence of the Q wave and its amplitude in CHF-induced rats treated with L-arginine confirmed irreversible cardiac remodeling.

The P wave was slightly increased in CHF-induced rats, possibly indicating that the induced CHF minimally affected atrial contractility. L-arginine administration did not significantly influence P wave duration, and its amplitude remained slightly reduced in CHF-induced rats. These findings suggest that L-arginine did not prevent atrial remodelling associated with CHF progression.

The P-R interval increased by 17.2 % ($P \leq 0.05$) in CHF-induced rats, indicating delayed impulse transmission from the sinoatrial node through the atrioventricular node to the

ventricles. L-arginine administration shortened the P-R interval by 11.5 % ($P \leq 0.05$), suggesting improved atrial conduction.

The duration of the QRS complex, which reflects ventricular contraction, increased by 37.2 % ($P \leq 0.05$) in CHF-induced rats compared to the control group. This prolongation was likely due to impaired conduction in the atrioventricular node and hyperkalaemia. L-arginine administration reduced the QRS duration by 18.0 %, indicating partial restoration of ventricular conduction.

A 50.2 % ($P \leq 0.05$) decrease in R wave amplitude in CHF-induced rats indicated impaired ventricular conduction and hypertrophic myocardial changes. L-arginine did not restore R wave amplitude, further confirming structural myocardial remodeling.

The S wave amplitude increased by 101.2 % in CHF-induced rats; however, these changes were not statistically significant. L-arginine administration resulted in a 3.7-fold ($P \leq 0.05$) decrease in S wave amplitude, reducing it below control values.

The QT interval increased by 60.3 % ($P \leq 0.05$) in CHF-induced rats, reflecting significant ventricular repolarization abnormalities. Following L-arginine treatment, QT interval duration decreased by 23.1 % ($P \leq 0.05$), suggesting improved ventricular repolarization.

In 45 % of CHF-induced rats, an upward-sloping ST segment depression was observed. As previously mentioned, this depression is associated with increased sympathetic nervous system activity as a compensatory mechanism in CHF. A key marker of heightened sympathetic tone is the reduction in T wave amplitude. In CHF-induced rats, T wave amplitude was 192.9 % ($P \leq 0.05$) lower than in the control group, indicating parasympathetic suppression. Following L-arginine administration, T wave amplitude increased by 25.0 % ($P \leq 0.05$). This suggests that L-arginine modulates sympathetic nervous system activity in CHF.

3.2. Discussion

In the chronic heart failure (CHF) model, there was an increase in AST and ALT activity, with AST elevation being more pronounced. This is because ALT is primarily found in the liver, whereas AST is localized in both the liver and myocardium. Several studies (Weng et al., 2015; Yokoyama et al., 2016) have reported AST elevation in cardiac pathologies, associating it with myocardial tissue damage, including in CHF.

The obtained data do not exclude the presence of liver pathology, particularly in cases of increased ALT levels. A separate study (Alvarez & Mukherjee, 2011) describes elevated AST and ALT levels in CHF, either due to passive congestion resulting from elevated filling pressures or due to low cardiac output leading to impaired perfusion.

One of the most distinct differential markers of left-sided CHF in its decompensated stage compared to right-sided CHF is the LDH index. In right-sided CHF, LDH levels increase approximately 2–3 times, whereas in left-sided CHF, the changes are generally less pronounced due to lower tissue damage and cell destruction. However, the present study established that L-arginine did not significantly alter LDH activity.

The observed increase in creatinine and urea concentrations in the blood of CHF rats is associated with the development of cardiorenal syndrome, a common CHF complication due to RAAS activation (Orvalho & Cowgill, 2017; Al-Naher et al., 2017).

The renin-angiotensin-aldosterone system (RAAS) is one of the most critical hormonal systems controlling cardiovascular, renal, and adrenal functions, regulating blood pressure, fluid volume, and electrolyte balance. A study by Hartupee and Mann (2016) explains that in the short term, RAAS activation induces several adaptive changes in the heart, kidneys, and vascular network aimed at maintaining cardiovascular homeostasis. However, prolonged activation leads to hemodynamic stress and exerts detrimental effects on the heart and circulation.

Electrolyte imbalance is crucial in the clinical course of CHF, as its alterations may necessitate therapeutic adjustments and are associated with prognosis. Common electrolyte disturbances in CHF include hyponatremia, hypokalaemia, and hypomagnesemia. Reduced cardiac output directly leads to decreased renal blood flow, impairing fluid and electrolyte excretion. This triggers multiple neurohormonal responses that influence both cardiovascular homeostasis and electrolyte balance (Urso et al., 2015).

An increased heart rate in CHF rats serves as a compensatory mechanism to maintain cardiac output. ECG analysis demonstrated heart rate elevation in most CHF model rats. In cases of atrial fibrillation, L-arginine had a notable effect in restoring rhythm, likely due to its role as an endogenous antifibrillatory agent (Andelova et al., 2022).

Under physiological conditions, impulse generation is initiated by the sinoatrial node and sequentially conducted through the atrial myocardium to the atrioventricular node, the bundle of His, its right and left branches, and Purkinje fibers within the ventricular myocardium. The basal heart rate is determined by this intrinsic conduction system and is regulated by autonomic (sympathetic and parasympathetic) cardiac innervation.

In some CHF rats, P wave duration and amplitude were reduced. Similar P wave alterations indicate left atrial remodeling and myocardial hypertrophy in CHF model rats. In this study, L-arginine did not significantly affect atrial excitability, leading to a further decrease in P wave amplitude under its administration.

A notable ECG characteristic in healthy rats is the absence of a Q wave. However, in the CHF model, a Q wave appeared, likely triggered by hypertrophic changes in the ventricular walls.

Under physiological conditions, L-arginine bioavailability is closely linked to age, sex, diet, body mass, and comorbid conditions such as inflammatory bowel diseases, irritable bowel syndrome, and malabsorption (Suzuki et al., 2017). The present study demonstrated that L-arginine contributed not only to the restoration of biochemical blood composition but also to electrolyte balance in CHF rats. These findings confirm the role of L-arginine in supporting myocardial function under pathological conditions.

4. Conclusions

This study demonstrated that the mesatone-induced CHF model effectively replicates key pathological features of heart failure, including structural myocardial remodeling, biochemical imbalances, and electrocardiographic abnormalities. Left-sided CHF was associated with myocardial hypertrophy, while right-sided CHF led to ventricular dila-

tion and fluid accumulation, indicating systemic dysfunction.

Biochemical analysis confirmed significant cardiac and renal impairment, with elevated markers of myocardial stress and electrolyte imbalances linked to neurohormonal activation. Electrocardiographic changes, including conduction delays and ventricular repolarization disturbances, reflected the progressive nature of CHF-related cardiac remodeling.

L-arginine administration showed cardioprotective effects by partially normalizing biochemical markers, improving renal function, and modulating electrolyte levels. Its impact on myocardial conduction suggests a potential role in mitigating CHF-related electrophysiological disturbances. However, while L-arginine demonstrated beneficial effects, it did not reverse structural myocardial changes, indicating the need for further investigation into its therapeutic applications in CHF.

Conflict of interest

The authors declare that there is no conflict of interest.

References

Acevedo, M., Valentino, G., Kramer, V., Bustamante, M. J., Adasme, M., Orellana, L., Baraona, F., & Navarrete, C. (2017). Superioridad del nuevo puntaje de riesgo ACC/AHA 2013 por sobre el puntaje de Framingham, en la predicción de riesgo de mortalidad cardiovascular en Santiago. *Revista Médica de Chile,* 145(3), 292–298.
[Crossref] [Google Scholar]

Al-Naher, A., Wright, D., Devonald, M. A. J., & Pirmohamed, M. (2017). Renal function monitoring in heart failure – what is the optimal frequency? A narrative review. *British Journal of Clinical Pharmacology,* 84(1), 5–17.
[Crossref] [Google Scholar]

Alvarez, A., & Mukherjee, D. (2011). Liver Abnormalities in Cardiac Diseases and Heart Failure. *International Journal of Angiology*, 20(03), 135–142.
[Crossref] [Google Scholar]

Andelova, K., Bacova, B. S., Sykora, M., Hlivak, P., Barancik, M., & Tribulova, N. (2022). Mechanisms Underlying Antiarrhythmic Properties of Cardioprotective Agents Impacting Inflammation and Oxidative Stress. *International Journal of Molecular Sciences*, 23(3), 1416.
[Crossref] [Google Scholar]

Antonenko, P. P., Zazharskyi, V. V., Suslova, N. I., Sklyarov, P. M., Reshetnichenko, O. P., Kostyuk, V. K., & Mylostyvyi, R. V. (2020). Efficacy of herbal essential oils at tetrachloromethane induced hepatitis in laboratory rats. *World of Medicine and Biology,* 16(73), 149.
[Crossref] [Google Scholar]

Arvanitaki, A., Michou, E., Kalogeropoulos, A., Karvounis, H., & Giannakoulas, G. (2020). Mildly symptomatic heart failure with reduced ejection fraction: diagnostic and therapeutic considerations. *ESC Heart Failure*, 7(4), 1477–1487.
[Crossref] [Google Scholar]

Bahls, M., Atzler, D., Markus, M. R. P., Friedrich, N., Böger, R. H., Völzke, H., Felix, S. B., Schwedhelm, E., & Dörr, M. (2018). Low-Circulating Homoarginine is Associated with Dilatation and Decreased Function of the Left Ventricle in the General Population. *Biomolecules*, 8(3), 63.
[Crossref] [Google Scholar]

European convention for the protection of vertebrate animals used for research and other scientific purposes (1986, March).
[Abstract] [Google Scholar]

Greene, S. J., Bauersachs, J., Brugts, J. J., Ezekowitz, J. A., Lam, C. S. P., Lund, L. H., Ponikowski, P., Voors, A. A., Zannad, F., Zieroth, S., & Butler, J. (2023). Worsening Heart Failure: Nomenclature, Epidemiology, and Future Directions. *Journal of the American College of Cardiology,* 81(4), 413–424.
[Crossref] [Google Scholar]

Hartupee, J., & Mann, D. L. (2016). Neurohormonal activation in heart failure with reduced ejection fraction. *Nature Reviews Cardiology*, 14(1), 30–38.
[Crossref] [Google Scholar]

Hsu, C.-N., & Tain, Y.-L. (2020). Amino Acids and Developmental Origins of Hypertension. *Nutrients*, 12(6), 1763.
[Crossref] [Google Scholar]

Huang, C., Qiu, S., Fan, X., Jiao, G., Zhou, X., Sun, M., Weng, N., Gao, S., Tao, X., Zhang, F., & Chen, W. (2021). Evaluation of the effect of Shengxian Decoction on doxorubicin-induced chronic heart failure model rats and a multicomponent comparative pharmacokinetic study after oral administration in normal and model rats. *Biomedicine & Pharmacotherapy*, 144, 112354.
[Crossref] [Google Scholar]

Lieshchova, M. A., Bilan, M. V., Evert, V. V., Kravtsova, M. V., & Mylostyvyi, R. V. (2022). Morphofunctional state of the rat's liver under the influence of Aralia elata alcohol tincture during the high-fat diet. *Scientific Messenger of LNU of Veterinary Medicine and Biotechnologies,* 24(108), 75–81.
[Crossref] [Google Scholar]

Lieshchova, M. A., Bilan, M. V., Mylostyvyi, R. V., Kravtsova, M. V., & Brygadyrenko, V. V. (2023). Effect of calcium propionate on rats with a high-fat hypercaloric diet. *Regulatory Mechanisms in Biosystems,* 14(4), 680–686.
[Crossref] [Google Scholar]

Orvalho, J. S., & Cowgill, L. D. (2017). Cardiorenal Syndrome. *Veterinary Clinics of North America: Small Animal Practice*, 47(5), 1083–1102.
[Crossref] [Google Scholar]

Otsuka, H., Abe, M., & Kobayashi, H. (2023). The Effect of Aldosterone on Cardiorenal and Metabolic Systems. *International Journal of Molecular Sciences,* 24(6), 5370.
[Crossref] [Google Scholar]

Schwinger, R. H. G. (2021). Pathophysiology of heart failure. *Cardiovascular Diagnosis and Therapy*, 11(1), 263–276.
[Crossref] [Google Scholar]

Suzuki, T., Morita, M., Hayashi, T., & Kamimura, A. (2017). The effects on plasma L-arginine levels of combined oral L-citrulline and L-arginine supplementation in healthy males. *Bioscience, Biotechnology, and Biochemistry*, 81(2), 372–375.
[Crossref] [Google Scholar]

Suzuki, Y. J. (2019). Oxidant-Mediated Protein Amino Acid Conversion. *Antioxidants*, 8(2), 50.
[Crossref] [Google Scholar]

Urso, C., Brucculeri, S., & Caimi, G. (2015). Acid–base and electrolyte abnormalities in heart failure: pathophysiology and implications. *Heart Failure Reviews,* 20(4), 493–503.
[Crossref] [Google Scholar]

Verveha, B. M., Gutyj, B. V., Lishchuk, S. H., Holubiev, M. I., & Mylostyvyi, R. V. (2023). Oxidative modification of proteins and antioxidant status in blood of the rats with experimental acute generalized peritonitis against the background of streptozotocin-induced diabetes. *Regulatory Mechanisms in Biosystems,* 14(2), 260–265.
[Crossref] [Google Scholar]

Weng, S. F., Kai, J., Guha, I. N., & Qureshi, N. (2015). The value of aspartate aminotransferase and alanine aminotransferase in cardiovascular disease risk assessment. *Open Heart*, 2(1), e000272.
[Crossref] [Google Scholar]

Yokoyama, M., Watanabe, T., Otaki, Y., Takahashi, H., Arimoto, T., Shishido, T., Miyamoto, T., Konta, T., Shibata, Y., Daimon, M., Ueno, Y., Kato, T., Kayama, T., & Kubota, I. (2016). Association of the Aspartate Aminotransferase to Alanine Aminotransferase Ratio with BNP Level and Cardiovascular Mortality in the General Population: The Yamagata Study 10-Year Follow-Up. *Disease Markers*, 2016, 1–9. [Crossref] [Google Scholar]

Zhou, Y., Zhao, Q., Liu, Z., & Gao, W. (2024). Blood urea nitrogen/creatinine ratio in heart failure: Systematic review and meta-analysis. *PLOS ONE*, 19(5), e0303870. [Crossref] [Google Scholar]

Ziaeian, B., & Fonarow, G. C. (2016). Epidemiology and aetiology of heart failure. *Nature Reviews Cardiology,* 13(6), 368–378. [Crossref] [Google Scholar]