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ADAPTIVE ACTION OF HEART CRYOEXTRACT ON MYOCARDIAL ENERGY METABOLISM IN EXPERIMENTAL EPINEPHRINE-INDUCED MYOCARDIODYSTROPHY

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Background. Myocardial energy homeostasis disruption plays a critical role in the development and progression of cardiovascular diseases. Epinephrine-induced myocardial dystrophy (EMD) serves as a relevant experimental model for studying the effects of sympathetic overactivation on myocardial tissue, including mitochondrial dysfunction, oxidative stress, and impaired carbohydrate metabolism.

Objective. This study aimed to elucidate the adaptive effects of porcine heart cryoextract on myocardial energy metabolism in a rat model of EMD.

Methods. Eighty-four male rats weighing 250–300 g were included in the study. EMD was induced by a single subcutaneous injection of 0.18% epinephrine tartrate solution at a dose of 5 mg/kg. Animals received intraperitoneal injections of cryoextract of porcine heart fragments (50 μg of peptides per 100 g of body weight) daily for 14 days. The control group received an equivalent volume of 0.9% sodium chloride solution. The reference group received amiodarone (10 mg/kg). Levels of adenine nucleotuides (ATP, ADP, and AMP) in myocardial tissue were determined using high-performance liquid chromatography, and the myocardial energy charge was calculated.

Results. Treatment with cardiac cryoextract led to a statistically significant increase in ATP content and myocardial energy charge compared to untreated controls. These findings suggest enhanced restoration of cellular energy metabolism and stabilization of the myocardial bioenergetic state under pathological conditions.

Conclusions. The study demonstrated that porcine cardiac cryoextract exhibits pronounced cardioprotective properties by improving myocardial energy processes in experimental myocardial dystrophy. These results support further research to explore its mechanisms of action and potential clinical applications in cardiology.

Keywords: epinephrine-induced myocardial dystrophy, cardiac cryoextract, energy metabolism, adenine nucleotides, energy charge.

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АДАПТАЦІЙНА ДІЯ КРІОЕКСТРАКТУ СЕРЦЯ НА ЕНЕРГЕТИЧНІ ПРОЦЕСИ В МІОКАРДІ ПРИ ЕКСПЕРИМЕНТАЛЬНІЙ АДРЕНАЛІНОВІЙ МІОКАРДІОДИСТРОФІЇ

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У роботі наведено результати дослідження впливу кріоекстракту серця на енергетичні процеси у міокарді при експериментальній адреналіновій міокардіодистрофії (АМД). На моделі АМД, створеній шляхом підшкірного введення адреналіну тартрату щурам-

самцям, оцінювали ефекти введення кріоекстракту фрагментів серця поросят. Проведено аналіз рівнів аденілових нуклеотидів (АТФ, АДФ, АМФ) та енергетичного заряду серця як критеріїв функціонування енергетичного обміну. Отримані результати свідчать про здатність кріоекстракту нормалізувати енергетичний баланс у серцевій тканині за умов патології. Зростання рівня АТФ та енергетичного заряду після введення екстракту порівняно з контролем вказує на активацію відновлювальних процесів. Виявлені ефекти підкреслюють перспективність подальшого вивчення механізмів дії кріоекстракту серця та можливості його клінічного застосування у кардіології.

Ключові слова: адреналінова міокардіодистрофія, кріоекстракт серця, енергетичний обмін, аденілові нуклеотиди, енергетичний заряд.

Introduction

One of the key mechanisms in the pathogenesis of many cardiovascular diseases is the disruption of energy homeostasis in the myocardium, which is accompanied by increased oxidative stress, mitochondrial dysfunction, and alterations in cardiomyocyte metabolism. Such changes are observed both in the context of generalized atherosclerosis [1, 2] and under conditions of excessive stress load, which becomes particularly relevant in wartime conditions [3].

Epinephrine-induced myocardial dystrophy (EMD) is considered in this context as an experimental model that reproduces myocardial injury under conditions of excessive activation of the sympathoadrenal system [4, 5]. Although this condition does not have the status of a separate clinical entity in the International Classification of Diseases (ICD), it reflects typical mechanisms underlying such clinical conditions as heart failure, coronary artery disease, and stress-induced cardiomyopathy [6, 7].

In this regard, there is growing scientific interest in the search for cardioprotective agents capable of correcting key pathobiochemical disturbances, in particular by reducing oxidative stress and normalizing cellular energy metabolism [8]. The contemporary concept of cardioprotection is undergoing a shift from symptomatic treatment to regenerative strategies, in which regulators of cellular metabolism and tissue adaptation play a central role [9]. In this context, natural extracts, among which cardiac cryoextract is notable, are considered promising cardioprotective agents with potential for metabolic and antioxidant modulation [10].

Objective: To investigate the mechanisms of the adaptive action of cardiac cryoextract on myocardial energy metabolism in a model of EMD.

Materials and methods

Experimental studies were conducted on 84 nonlinear male white rats weighing 250–300 g, maintained under standard vivarium conditions. Epinephrine-induced myocardial dystrophy was modeled by a single subcutaneous injection of 0.18% epinephrine tartrate solution at a dose of 5 mg/kg, using the method described by Markova [4]. Animals were randomly assigned to four groups (n = 21 each): intact (no intervention), control (EMD without treatment), experimental (EMD + cardiac cryoextract), and reference (EMD + amiodarone). In each group, 7 animals were sacrificed on days 2, 7, and 14 of observation.

The cryoextract from porcine heart fragments (CCE), also referred to as cardiac cryoextract, was prepared according to a previously described method [10]. The extract was administered intraperitoneally at a dose of 50 µg of peptides per 100 g of body weight daily for 14 days. The control group received isotonic NaCl solution, while the reference group was treated with amiodarone at a dose of 10 mg/kg.

At the end of the experiment, heart tissue and blood samples were collected. Preparation of cardiac tissue homogenates, plasma and serum isolation, as well as determination of adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP) levels and calculation of the energy charge (EC), were performed according to previously described methods [11, 12]. The EC was calculated according to Atkinson [11], using the formula: EC = (ATP + 0.5 ADP) / (ATP + ADP + AMP).

The study was conducted in accordance with the fundamental bioethical principles outlined in the European Union Directive 2010/63/EU on the protection of animals used for scientific purposes, as well as other applicable national and international regulations. The research protocol was reviewed and approved by the Bioethics Committee of the Institute for Problems of Cryobiology and Cryomedicine of the National Academy of Sciences of Ukraine (Protocol No. 2, January 3, 2022).

Statistical analysis. Statistical processing of the results was performed using Microsoft Excel (Microsoft Office package). The distribution of variables within each group was assessed using the Shapiro–Wilk test. For normally distributed independent variables, between-group differences were evaluated pairwise using Student's *t*-test. For non-normally distributed data in at least one group, pairwise comparisons were performed using the nonparametric Mann–Whitney *U*-test. Differences were considered statistically significant at $p < 0.05$.

Results and discussion

The study demonstrated that ATP levels in rat cardiac tissue during the development of EMD undergo significant changes depending on the therapeutic approach applied, particularly following the administration of CCE (Table 1).

In rats with the EMD model, a significant decrease in ATP content in cardiac tissue was observed as early as Day 2. Administration of CCE led to a significant increase in ATP levels compared to untreated animals, suggesting early activation of energy metabolism. A similar, albeit slightly less pronounced, effect was observed with amiodarone.

By Day 7, all treatment groups showed an increase in ATP levels, with the highest values observed in animals receiving CCE. The difference between CCE and amiodarone was not statistically significant, although both agents exceeded the control group in the degree of energy metabolism recovery.

By Day 14, ATP levels in the CCE group approached those of intact animals. Recovery was also observed in the amiodarone and untreated groups, but to a lesser extent. At all-time points, the dynamics in the CCE group were

Table 1

Effect of cryoextract of porcine heart fragments on adenosine triphosphate levels in rat cardiac tissue in a model of epinephrine-induced myocardial dystrophy, μmol/g dry tissue (M±m, 95% CI, n=84)

Time points	Group I	Group II	Group III	Group IV	P-value [Δ%]			
	Intact rats	Controls (EMD without treatment)	EMD + CCE	EMD+ amiodarone (10 mg/kg)	p_{2-1}	p_{3-2}	p_{4-2}	p_{4-3}
Day 2	3.7±0.06 (95% CI: 3.5–3.8)	1.2±0.09 (95% CI: 1.0–1.4)	1.5±0.04 (95% CI: 1.4–1.5)	1.7±0.06 (95% CI: 1.5–1.8)	<0.0001 [66.8%]	0.03 [20.0%]	0.002 [36.5%]	0.02 [13.7%]
Day 7	3.4±0.10 (95% CI: 3.2–3.6) p_{d2} = 0.04 [-7.4%]^{d2}	1.8±0.06 (95% CI: 1.7–1.9) p_{d2} = 0.009 [45.9%]^{d2}	2.4±0.13 (95% CI: 2.1–2.6) p_{d2} = 0.009 [63.7%]^{d2}	2.2±0.06 (95% CI: 2.0–2.3) p_{d2} = 0.009 [30.2%]^{d2}	<0.001 [47.7%]	0.001 [34.7%]	0.001 [21.8%]	0.1 [9.6%]
Day 14	3.8±0.06 (95% CI: 3.7–3.9) p_{d2} = 0.02 [3.52%]^{d2} p_{d7} = 0.01 [11.8%]^{d7}	2.9±0.07 (95% CI: 2.8–3.0) p_{d2} = 0.01 [140.0%]^{d2} p_{d7} = 0.01 [64.5%]^{d7}	3.3±0.07 (95% CI: 3.1–3.4) p_{d2} = 0.01 [125.5%]^{d2} p_{d7} = 0.01 [37.7%]^{d7}	3.0±0.15 (95% CI: 2.7–3.3) p_{d2} = 0.01 [80.7%]^{d2} p_{d7} = 0.01 [38.4%]^{d7}	<0.001 [23.0%]	0.003 [12.7%]	<0.001 [2.5%]	0.1 [9.1%]

Notes (applicable to Tables 1–4):

1. p_{2-1} – level of statistical significance;
2. [Δ%] – percentage differences;
3. Indices 1, 2, and 3 denote the groups being compared;
4. Indices $_{d2}$, $_{d7}$ denote study days compared over time.

significantly better than in the control group, indicating a potentially pronounced energotropic effect of CCE.

In animals with EMD, a significant increase in ADP levels in cardiac tissue was observed, indicating disruption of energy homeostasis (Table 2).

Administration of CCE as early as Day 2 led to a significant reduction in this parameter compared to the untreated control animals.

By Day 7, the treatment groups continued to show a trend toward decreased ADP levels, whereas in the control group, levels remained elevated. CCE produced a more consistent reduction over time compared with amiodarone, although the difference between these two groups was not statistically significant.

By Day 14, ADP concentrations decreased in all treatment groups, with levels in the CCE group approaching those of intact animals. In the control group, despite partial normalization, levels remained elevated, indicating that CCE more effectively restored normal adenine nucleotide balance.

Table 2

Effect of cryoextract of porcine heart fragments on adenosine diphosphate levels in rat cardiac tissue in a model of epinephrine-induced myocardial dystrophy, μmol/g dry tissue (M±m, 95% CI, n=84)

Time points	Group I	Group II	Group III	Group IV	P-value [Δ%]			
	Intact rats	Controls (EMD without treatment)	EMD + CCE	EMD+ amiodarone (10 mg/kg)	p_{2-1}	p_{3-2}	p_{4-2}	p_{4-3}
Day 2	1.1±0.06 (95% CI: 0.9–1.2)	2.1±0.05 (95% CI: 2.0–2.2)	1.6±0.04 (95% CI: 1.5–1.7)	1.6±0.10 (95% CI: 1.4–1.8)	<0.001 [101.4%]	<0.001 [24.8%]	0.001 [24.2%]	0.9 [0.9%]
Day 7	1.2±0.03 (95% CI: 1.1–1.3) p_{d2} = 0.05 [13.5%]^{d2}	1.8±0.09 (95% CI: 1.7–2.0) p_{d2} = 0.02 [14.1%]^{d2}	1.5±0.04 (95% CI: 1.4–1.5) p_{d2} = 0.02 [8.0%]^{d2}	1.4±0.06 (95% CI: 1.3–1.5) p_{d2} = 0.06 [15.0%]^{d2}	<0.001 [52.4%]	0.003 [19.5%]	0.001 [25.0%]	0.2 [6.8%]
Day 14	1.1±0.08 (95% CI: 0.9–1.2) p_{d2} = 0.5 [-]^{d2} p_{d7} = 0.06 [-11.9%]^{d7}	1.4±0.08 (95% CI: 1.3–1.6) p_{d2} = 0.01 [-32.2%]^{d2} p_{d7} = 0.01 [-21.1%]^{d7}	1.3±0.05 (95% CI: 1.2–1.4) p_{d2} = 0.02 [-17.9%]^{d2} p_{d7} = 0.02 [-10.7%]^{d7}	1.4±0.04 (95% CI: 1.4–1.5) p_{d2} = 0.6 [-10.6%]^{d2} p_{d7} = 0.3 [5.2%]^{d7}	0.006 [36.5%]	0.2 [8.9%]	0.006 [-]	0.06 [9.8%]

The study of CCE effects on AMP levels in rat cardiac tissue in the EMD model also revealed significant changes in this parameter depending on the type of treatment and the study time point (Table 3).

In animals with EMD, a marked increase in AMP levels was observed, indicating energy depletion. Administration of CCE or amiodarone led to a significant reduction in AMP concentration as early as Day 2, with further stabilization by Day 7. The decrease was more pronounced in the CCE group.

By Day 14, AMP levels in all treatment groups approached physiological values. In animals receiving CCE, the parameter decreased significantly at an early stage and remained stable until the end of the study. The control group showed only partial recovery. Thus, CCE demonstrated effective activity in normalizing energy balance, particularly by reducing excess AMP.

Assessment of EC in cardiac tissue of rats with EMD revealed significant changes depending on the study time points and applied treatment. On Day 2 after EMD induction, EC decreased significantly, indicating impaired myocardial energy status. Administration of CCE and amiodarone promoted partial recovery, with better results observed in the amiodarone group.

By Day 7, EC levels in both treatment groups were substantially higher than in untreated animals. CCE showed a slightly better trend compared with amiodarone, although no statistically significant difference was observed.

By Day 14, EC continued to increase in all groups. In animals receiving CCE, levels approached those of intact rats, indicating effective restoration of energy homeostasis. Amiodarone also promoted EC elevation, although the effect was less pronounced compared with CCE (Table 4).

The results of this study demonstrate a pronounced positive effect of CCE on the regulation of myocardial energy metabolism in rats with EMD. At early stages, specifically on Day 2 post-EMD induction, a significant decrease in ATP levels was observed in the cardiac tissue of the control group, confirming an acute energy deficit due to destructive myocardial processes. Administration of CCE resulted in significant increase in ATP levels compared with untreated controls, suggesting activation of energy-generating mechanisms and stabilization of metabolic homeostasis.

Over the course of the study, on Days 7 and 14, a gradual restoration of energy metabolism parameters was observed in all groups. In rats receiving CCE, ATP levels increased more markedly and approached the levels observed in intact animals, indicating more effective regeneration of energetic capacity. Although amiodarone also showed a positive trend, its efficacy was somewhat lower than that of CCE, as evidenced by both absolute ATP values and statistical analyses.

Additionally, assessment of ADP and AMP levels demonstrated a reduction in their concentrations under CCE treatment, indicates restoration of the normal adenine nucleotide balance and activation of ATP resynthesis. The decline in AMP was particularly notable, as AMP levels were significantly elevated in the control group under hypoxic and metabolic stress. This effect in the CCE group may be interpreted as an indicator of normalized oxidative phosphorylation.

Evaluation of energy charge (EC) as an integrative indicator of energy metabolism further confirmed the advantages of CCE administration. At an early stage of treatment, EC in the CCE group was significantly higher compared to the control group, and by Day 14, it nearly reached levels observed in intact rats. This suggests effective stabilization of myocardial energy balance following CCE administration, likely mediated by the biologically active components of the preparation with metabolic, antioxidant, and membrane-stabilizing effects. These findings are consistent with previously established antioxidant properties of CCE [12]. Future studies should investigate the effects of the cryoextract under systemic pathological conditions, including extracoronary vascular involvement,

Table 3

Effect of cryoextract from porcine heart fragments on adenosine monophosphate levels in rat cardiac tissue in a model of epinephrine-induced myocardial dystrophy, μmol/g dry tissue (M±m, 95% CI, n=84)

Time points	Group I	Group II	Group III	Group IV	P-value [Δ%]			
	Intact rats	Controls (EMD without treatment)	EMD + CCE	EMD+ amiodarone (10 mg/kg)	p_{2-1}	p_{3-2}	p_{4-2}	p_{4-3}
Day 2	0.5±0.001 (95% CI: 0.52–0.54)	1.2±0.05 (95% CI: 1.1–1.3)	1.0±0.08 (95% CI: 0.8–1.2)	0.9±0.11 (95% CI: 0.7–1.1)	<0.001 [128.5%]	0.05 [17.7%]	0.02 [28.2%]	0.4 [12.9%]
Day 7	0.5±0.01 (95% CI: 0.49–0.53) p_{d2} = 0.05 [-4.3%]^{d2}	1.0±0.06 (95% CI: 0.9–1.1) p_{d2} = 0.03 [-17.6%]^{d2}	0.6±0.09 (95% CI: 0.4–0.8) p_{d2} = 0.009 [-38.6%]^{d2}	0.7±0.12 (95% CI: 0.4–0.9) p_{d2} = 0.1 [-23.0%]^{d2}	<0.001 [96.6%]	0.004 [38.6%]	0.03 [32.9%]	0.7 [9.3%]
Day 14	0.5±0.01 (95% CI: 0.47–0.52) p_{d2} = 0.01 [-7.3%]^{d2} p_{d7} = 0.2 [-3.9%]^{d7}	0.6±0.06 (95% CI: 0.5–0.7) p_{d2} = 0.01 [-49.4%]^{d2} p_{d7} = 0.01 [-38.6%]^{d7}	0.5±0.07 (95% CI: 0.4–0.7) p_{d2} = 0.01 [-45.7%]^{d2} p_{d7} = 0.2 [-11.6%]^{d7}	0.5±0.03 (95% CI: 0.6–0.6) p_{d2} = 0.01 [-41.0%]^{d2} p_{d7} = 0.2 [-23.4%]^{d7}	0.05 [24.6%]	0.4 [11.6%]	0.05 [16.3%]	0.7 [5.3%]

Table 4

Effect of cryoextract from porcine heart fragments on energy charge in rat heart tissue in an adrenaline-induced myocardial dystrophy model (M±m, 95% CI, n=84)

Time point	Group I	Group II	Group III	Group IV	P-value [Δ%]			
	Intact rats	controls (EMD without treatment)	EMD + CCE	EMD+ amiodarone (10 mg/kg)	p_{2-1}	p_{3-2}	p_{4-2}	p_{4-3}
Day 2	0.80±0.02 (95% CI: 0.79–0.80)	0.50±0.01 (95% CI: 0.48–0.52)	0.56±0.01 (95% CI: 0.54–0.58)	0.60±0.01 (95% CI: 0.57–0.63)	<0.001 [37.4%]	0.004 [11.7%]	<0.001 [19.9%]	0.04 [7.4%]
Day 7	0.78±0.04 (95% CI: 0.78–0.79) p_{d2} = 0.009 [-2.0%]^{d2}	0.58±0.01 (95% CI: 0.56–0.60) p_{d2} = 0.009 [16.1%]^{d2}	0.70±0.02 (95% CI: 0.67–0.73) p_{d2} = 0.009 [25.3%]^{d2}	0.68±0.02 (95% CI: 0.65–0.70) p_{d2} = 0.03 [13.6%]^{d2}	<0.001 [25.9%]	<0.001 [20.6%]	<0.001 [17.3%]	0.4 [3.5%]
Day 14	0.81±0.01 (95% CI: 0.80–0.82) p_{d2} = 0.06 [1.35%]^{d2} p_{d7} = 0.01 [3.41%]^{d7}	0.73±0.01 (95% CI: 0.71–0.76) p_{d2} = 0.01 [46.7%]^{d2} p_{d7} = 0.01 [26.3%]^{d7}	0.77±0.01 (95% CI: 0.74–0.79) p_{d2} = 0.01 [37.7%]^{d2} p_{d7} = 0.01 [9.9%]^{d7}	0.75±0.01 (95% CI: 0.74–0.76) p_{d2} = 0.01 [25.2%]^{d2} p_{d7} = 0.01 [10.2%]^{d7}	0.001 [9.5%]	0.049 [4.9%]	0.001 [2.3%]	0.1 [2.4%]

as previous work has highlighted the importance of systemic vascular pathology in cardiovascular disease [13].

Building on the observed dynamics of ATP, ADP, AMP, and energy charge, the results indicate that CCE exerts a multifactorial effect on myocardial energy homeostasis in the EMD model. The observed increase in ATP levels, concomitant with reductions in ADP and AMP concentrations under CCE treatment, may reflect not merely compensation for energy deficit but a deeper activation of high-energy phosphate resynthesis systems. This effect is likely mediated through enhanced efficiency of oxidative phosphorylation and preservation of mitochondrial membrane integrity, which is particularly critical under conditions of oxidative stress.

Notably, the changes observed with CCE exhibited a preventive factor: restoration of energy parameters began earlier and progressed more rapidly than with amiodarone. This suggests that the biologically active components of CCE may influence cellular regulatory systems, including activation of AMP-activated protein kinase (AMPK), a key energy sensor, and stimulation of mitochondrial biogenesis via PGC-1α–related signaling pathways.

Another important aspect is that CCE not only prevented early decreases in energy charge (EC) following myocardial injury but also promoted its gradual restoration toward physiological levels. From a pathophysiological perspective, this is highly significant: even transient loss of energetic balance in cardiomyocytes can trigger cascades of apoptosis and necrosis. Thus, the ability to stabilize myocardial energy status is effectively equivalent to the potential to prevent progression of heart failure.

Particular attention should be paid to the dynamic ATP/ADP/AMP ratio: following CCE administration, a restoration of the normal adenine nucleotide profile was observed, indicating optimization of the cellular energy cycle, recovery of adenylate kinase activity, and stabilization of the intracellular nucleotide pool. Importantly, this effect persisted even at later time points (Day 14), suggesting a prolonged action of the preparation.

Thus, interpretation of the obtained data allows us to hypothesize that CCE exerts a comprehensive cardioprotective effect, simultaneously delivering energy-modulating, antioxidant, and membrane-stabilizing actions. This multifactorial profile distinguishes CCE from conventional pharmacological agents, whose effects are typically targeted at individual components of the pathophysiological cascade.

In a broader biomedical context, these findings underscore the concept of using tissue-specific extracts of natural origin as agents for metabolic therapy in cardiology. Current understanding emphasizes that a key strategy in cardioprotection involves modulating the energetic and antioxidant potential of cardiomyocytes in response to diverse stressors, ranging from ischemic to catecholaminergic stress. Considering that myocardial injury resulting from ischemic, inflammatory, or toxic insults is characterized by energy imbalance and limited reparative capacity due to the low proliferative potential of cardiomyocytes, there is a strong rationale for therapeutic strategies that combine anti-inflammatory, metabolic, and regenerative properties [14]. Taken together, biologically derived formulations may be considered as agents with the capacity to restore organ function through stimulation of reparative processes. The similar research by Halchenko and Sandomirsky [15] demonstrated that extracts from cryopreserved organ fragments of pigs and piglets, including cardiac tissue, contain bioactive peptides that regulate cellular proliferation, thereby underscoring the broader potential of tissue-specific peptide formulations in cardioprotection. Moreover, cryobiological technologies enable the production of extracts with consistently high biological activity [12, 15].

Building on these findings, our results suggest that the use of CCE represents not merely a symptomatic approach to correcting energy disturbances, but a component of pathogenetic therapy with the potential to modify the course of cardiac diseases associated with metabolic dysfunction.

Conclusions

Cryoextract of porcine heart fragments effectively enhanced the restoration of ATP levels in the myocardial tissue of rats with epinephrine-induced myocardial dystrophy. By Day 14 of the experiment, ATP levels in the CCE group reached 3.3 ± 0.07 μmol/g of dry tissue, which was 13.8% lower than in intact animals (3.8 ± 0.06 μmol/g; $p < 0.001$) and 13.8% higher than in the control group (2.9 ± 0.07 μmol/g; $p < 0.001$).

CCE produced a significant improvement in cardiomyocyte energy charge (EC). By Day 14 of the experiment, EC in the CCE group reached 0.77 ± 0.01, which was 5.5% lower than that in intact rats (0.81 ± 0.01; $p = 0.001$) but 5.5% higher than in the control group (0.73 ± 0.01; $p = 0.049$).

Administration of CCE contributed to normalization of the adenylate nucleotide pool by reducing elevated ADP and AMP levels. Specifically, on Day 7, AMP levels in the CCE group were 0.6 ± 0.09 μmol/g, which was 38.6% lower than in the untreated control group (1.0 ± 0.06 μmol/g; $p = 0.004$), while ADP levels were 1.5 ± 0.04μmol/g, 19.5% lower than in the control ($p = 0.003$).

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