ORIGINAL ARTICLE

CONTENTS

Potential cardioprotective effect of trimetazidine in mice model of endotoxemia: role of AMPK-Nrf2

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ABSTRACT

Aim: To clarify the potential cardioprotective effect of Trimetazidine against experimentally sepsis-caused endotoxic cardiac injury damage in mice.

Materials and Methods: 24 Mice were divided into four groups (n=6): Sham group, CLP group DMSO group, trimetazidine-treated group 50 mg/kg IP, 1hr before CLP, then the animals were sacrificed 24 hr after CLP and tissue sample was taken for measurement of TNF-A, TNF-Ar1, IL-1β, HO-1, MPO, caspase-11, F2-isoprostane and serum troponin by ELISA and gene expression of AMPK-Nrf2 by qpcr and histopathological study.

Results: trimetazidine treated group showed significant changes as compared with clp group regarding TNF-α, TNF-αr1, IL-1β, HO-1, MPO, CASPASE-11, F2-ISOPROSTANE as well as affect tissue mRNA expression of AMPK-Nrf2 genes $p<0.05$.

Conclusions: We evaluate that Trimetazidine has cardio protective effects due to its anti-inflammatory and anti-oxidative action. Also, trimetazidine showed a cardio-protective effect as they affect tissue mRNA expression of AMPK-Nrf2 genes.

KEY WORDS: CLP, sepsis, trimetazidine, TNF-α, TNF-Ar1, IL-1β, Ho-1, MPO, caspase-11, F2-isoprostane

Wiad Lek. 2025;78(1):35-44. doi: 10.36740/WLek/190820 DOI

INTRODUCTION

Sepsis is characterized as a global healthcare concern, stemming from a systemic inflammatory response triggered by bacterial infection [1, 2]. Cardiac impairment stands as a significant outcome of sepsis, contributing to escalated mortality rates. This phenomenon has been linked to heightened inflammation, inhibition of both fatty acid and glucose oxidation, depletion of adenosine triphosphate (ATP), and impairment of the cardiac adrenergic response, which exacerbates cardiac function [3, 4]. In other words, sepsis may decrease cardiac work via a rise expression level of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6, which act as cardio depressant pro-inflammatory mediators resulting in cardiac contractile dysfunction, cardiac hypertrophy, and heart failure [5]. It has been documented findings that there is an increase in the production of these oxidant molecules during sepsis in many cells such as mitochondria and cardiomyocytes [5, 6]. Functioning as a detector of intracellular energy levels, AMPK serves as a crucial focal point for the regulation of inflammation. Emerging insights indicate that activating AMPK can mitigate oxidative stress and counteract inflammation [7]. The mechanistic links between AMPK and inflammation have primarily revolved around their relationship with the NF-κB pathway. Evidence shows that chemical activators of AMPK can diminish NF-κB-mediated transcription and AMPK activation can inhibit NF-κB signaling and consequent inflammation driven by fatty acids in macrophages, even though NF-κB subunits are not direct targets of AMPK [8, 9]. Given the well-established role of the Nrf2 pathway in mitigating oxidative stress and quelling inflammation, the potential for interactions between the Nrf2 and AMPK pathways has been acknowledged [10]. Trimetazidine inhibit β-oxidation of free fatty acid. By selectively inhibiting (LC 3-KAT (Has been found to have anti-apoptosis, anti-inflammatory, anti-oxidative and pleiotropic effects [11].

AIM

The aim of our research is to clarify the potential cardioprotective effect of Trimetazidine against experimentally sepsis-caused endotoxic cardiac injury damage in mice.

MATERIALS AND METHODS

The University of Kufa Department of Pharmacology and Therapeutics was the site of this study. All experiments were approved by Animal Care and Research

committee of the University of Kufa. Animals were housed in the animal house at University of Kufa.

STUDY DESIGN

Twenty-four adult males of Swiss white mice (weighting 20-30 g, aged 4-8 weeks) were purchased from the animal resource center, under conditions of 24°C ± 2°C with alternative 12-hrlight/12-hr dark cycles. The mice were also allowed to a free access to the water and diet until the start of experiment. Mice randomized into 4 groups (n=6): Sham group (laparotomy without CLP), CLP group, DMSO group and trimetazidine treated group (50mg/kg IP, 1hr before CLP, then the animals were sacrificed 24 hr after CLP).

EXPERIMENTAL PROCEDURE

The induction of sepsis was done via the cecal ligation and puncture model (CLP) based on previous studies [7, 8, 12]. In brief, an 18-G needle was employed in conjunction with the double puncture approach to induce organ (cardiac) dysfunction during the early stages of sepsis first 24 hours [9]. A small amount of stool was extracted to ensure the patency of the puncture sites. After this, the abdomen was sutured. All animals have received a subcutaneous resuscitative dose of normal saline (20 mL/kg body weight) to induce organ (cardiac) dysfunction during the early stages of sepsis first 24 hrs.

PREPARATION OF TRIMETAZIDINE

Powder was obtained from MedChem express company, and prepared in diluted DMSO 10%, then was given in a dose of 7.2 mg/kg i.p, 1 hr before CLP [13].

COLLECTION OF A TISSUE SAMPLES

At the end of the procedure (24 hours), mice were re-anesthetized with 20 mg/kg xylazine and 100 mg/kg ketamine. Blood sample was collected immediately from the heart. The blood samples were then centrifuged at 3000 RPM for 10 min. Serum was collected by centrifuging again at 3000 RPM for 1 minute to remove any red blood cells [14, 15]. The heart tissue was rinsed with an ice-cold saline to remove any red blood cells or clots and divided into 3 parts first part was kept at deep freeze for homogenization and ELISA study, second part was kept in RNA later solution at deep freeze until qRT-PCR testing was performed, whereas the remaining portion was formalin fixed until histopathological analysis was performed.

TISSUE HOMOGENIZATION FOR TNF-A, TNFAR, IL-1B, HO-1, CASPASE-11, MPO AND F2-ISOPROSTANE MEASUREMENT

Tissue homogenization technique was performed according to the previous studies [11].

TISSUE PREPARATION FOR HISTOPATHOLOGY

The heart tissue histopathology and scoring were performed according to Zingarelli protocol [16]

EXPRESSION OF AMPK- Nrf2 HEART TISSUE BY QRT-PCR

The mRNA expression of AMPK-Nrf2 is determined using a quantitative real-time PCR, as specified by the manufacturer. Real-time quantitative (RT-q) PCR-total RNA was extracted using special chemicals and instruments [16]. The primer sequences used for qRT-PCR Gene primer sequence is:

AMPKr: 5-GGTCCTGGTGGTTTCTGTTG-3'
AMPKf: 5-CTCTATGCTTTGCTTTGCTGTGTGG-'3
Nrf2r: 5-TGAGAGACTGGTCACACT-3'
Nrf2f: 5-CAGCATGATGGACTTGGA-3'

STATISTICAL ANALYSIS

Statistical analysis was performed using a IBM SPSS 24.0. Data were expressed as mean ± SEM. ANOVA was used for the multiple comparisons among all groups followed by Bonferroni's test. The Mann-Whitney U and Kruskal -Wallis tests were used to assess the histopathological changes, which were determined as, scores from 0 to 4. ($P<0.05$ was considered statistically significant difference).

RESULTS

Effect of trimetazidine on cardiac tissue level of TNF-α, TNFαR, IL-1β, HO-1, caspase-11, MPO and F2-isoprostane, data showed a significant elevation $p<0.05$ in TNF-α, TNFαR, IL-1β, HO-1, caspase-11, MPO and F2-isoprostane, in CLP and DMSO groups when compared with sham group. Additionally, trimetazidine group showed markedly decreased levels of these markers if compared with the CLP & DMSO groups (significant difference, P value <0.05). More interesting, level of serum troponin was significantly higher ($p<0.05$) in sepsis and DMSO groups as compared with the sham group. Additionally, trimetazidine group showed markedly reduced levels ($p<0.05$) of serum troponin when compared with sepsis and DMSO groups (significant difference P value <0.05) (Fig.1-8).

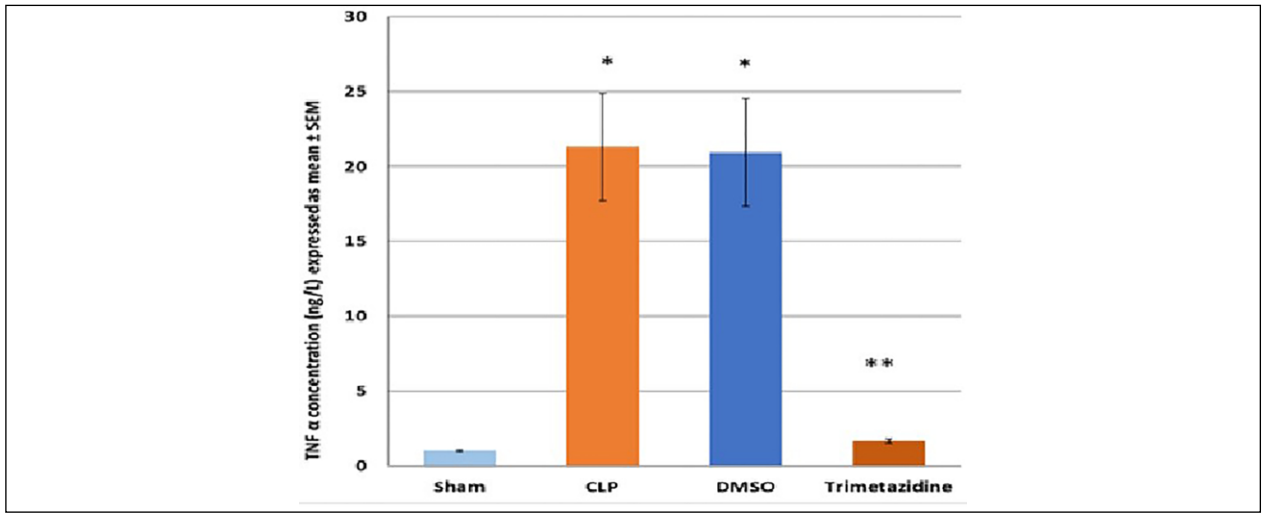

Fig. 1. Mean tissue level of TNF-α (ng/L) in 4 experimental groups 24 hours after sepsis. *: significant difference in CLP & DMSO as compare with the sham group; **: significant difference in pretreated group as compare with CLP group.

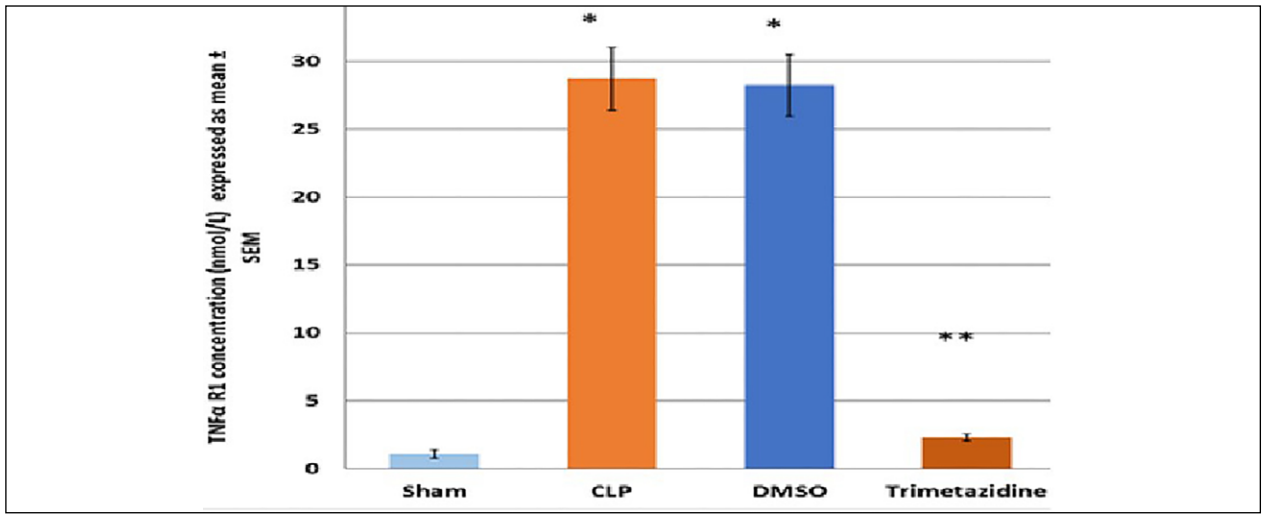

Fig. 2. Mean tissue level of TNF-αR1 (nmol/L) in 4 experimental groups 24 hours after sepsis. *: significant difference in CLP & DMSO as compare with the sham group; **: significant difference in pretreated group as compare with CLP group.

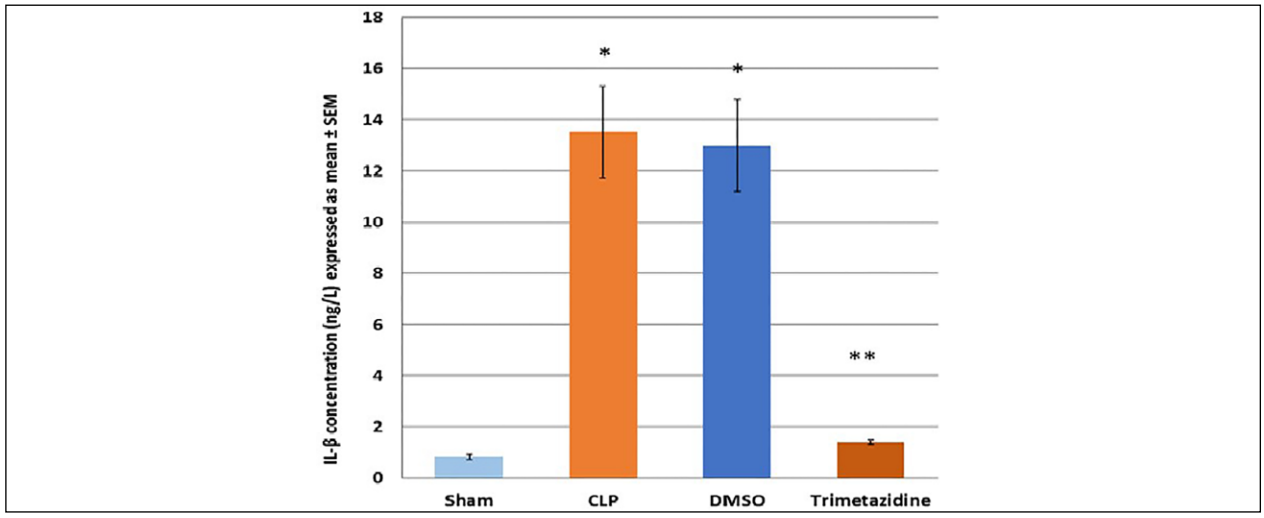

Fig. 3. Mean tissue level of IL- 1β (ng/L) in 4 experimental groups 24 hours after sepsis. *: significant difference in CLP & DMSO as compare with the sham group; **: significant difference in pretreated group as compare with CLP group.

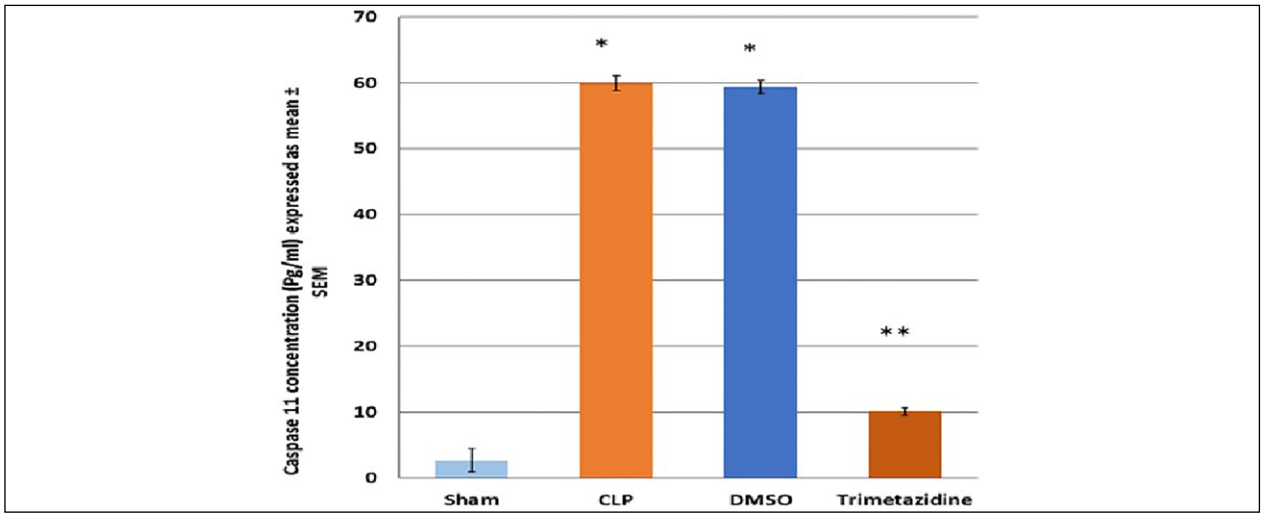

Fig. 4. Mean tissue level of caspase-11 (pg/ml) in 4 experimental groups 24 hours after sepsis. *: significant difference in CLP & DMSO as compare with the sham group; **: significant difference in pretreated group as compare with CLP group.

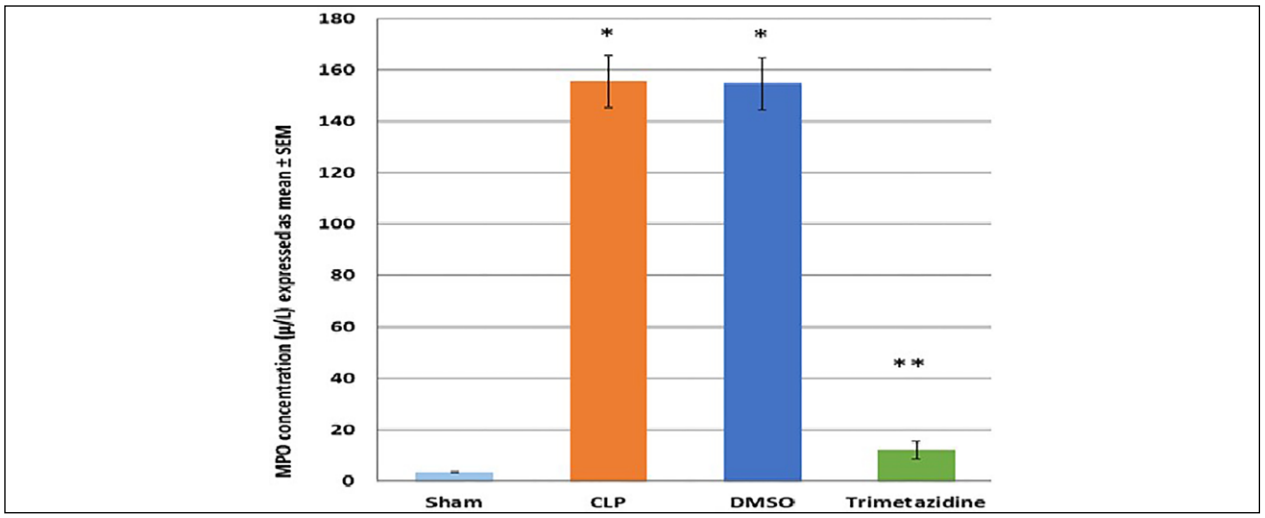

Fig. 5. Mean tissue level of MPO (µ/L) in 4 experimental groups 24 hours after sepsis. *: significant difference in CLP & DMSO as compare with the sham group; **: significant difference in pretreated group as compare with CLP group.

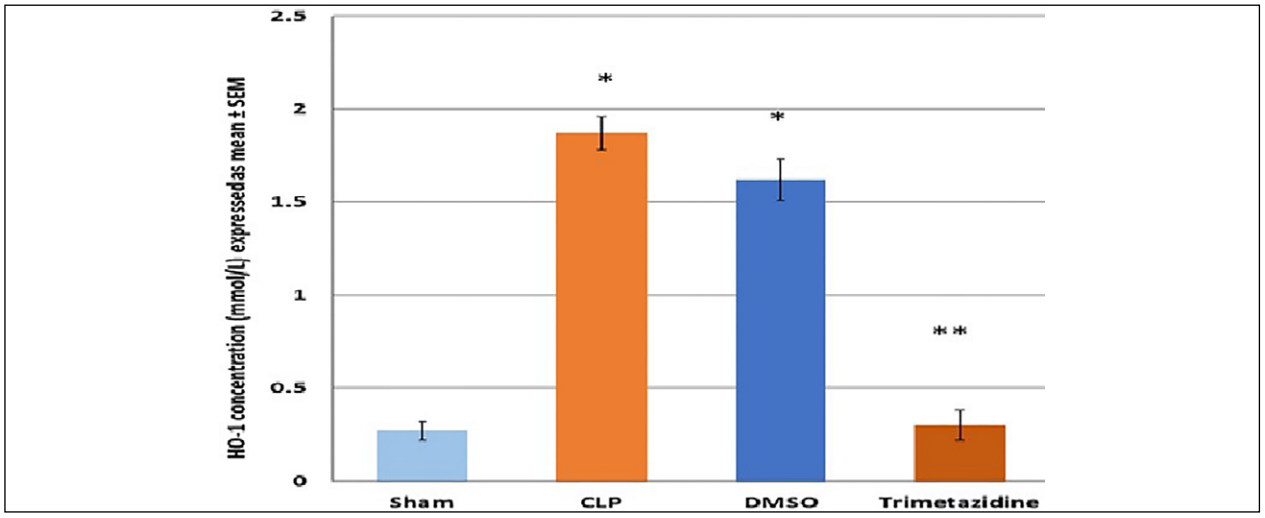

Fig. 6. Mean tissue level of HO-1 (mmol/L) in 4 experimental groups24 hours after sepsis. *: significant difference in CLP & DMSO as compare with the sham group; **: significant difference in pretreated group as compare with CLP group.

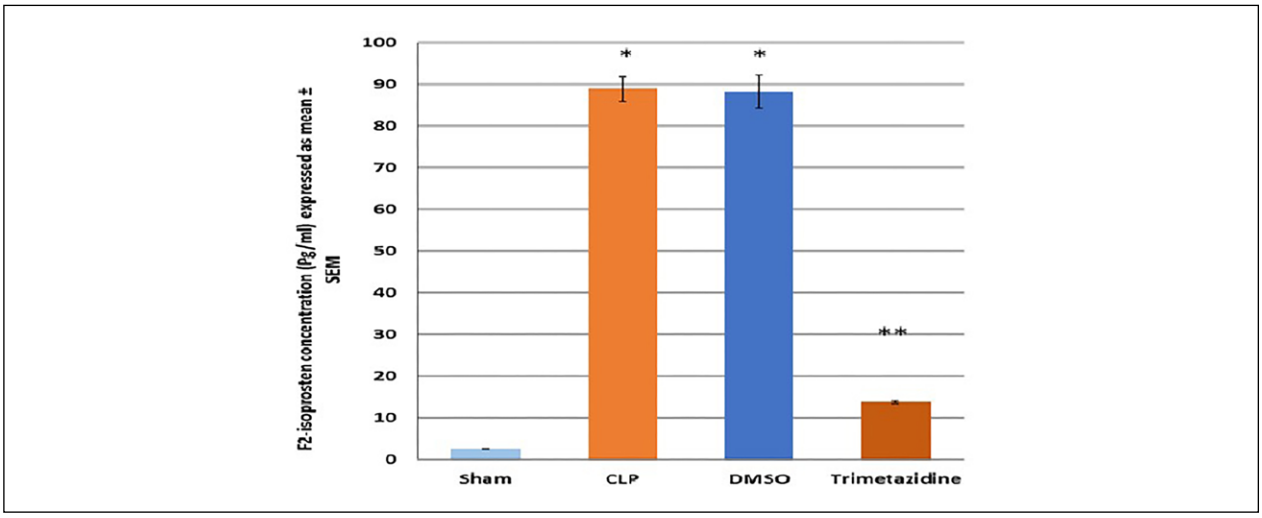

Fig. 7. Mean tissue level of F2- isoprostane (pg./L) in 4 experimental groups 24 hours after sepsis. *: significant difference in CLP & DMSO as compare with the sham group; **: significant difference in pretreated group as compare with CLP group.

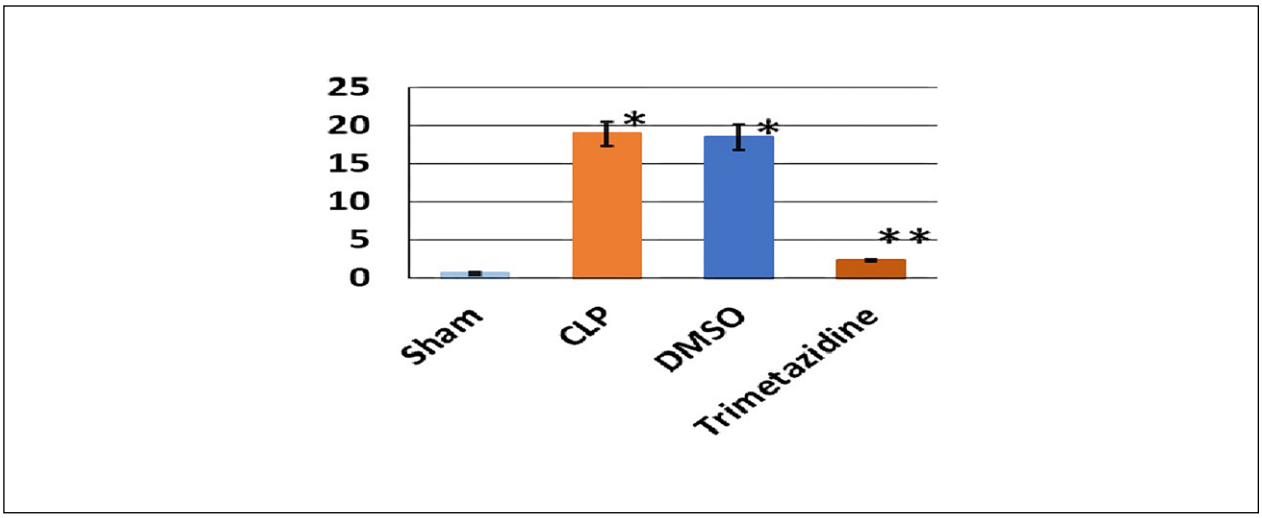

Fig. 8. Mean serum level of troponinn (pg/ml) in 4 experimental groups 24 hours after sepsis. *: significant difference in CLP & DMSO as compare with the sham group; **: significant difference in pretreated group as compare with CLP group.

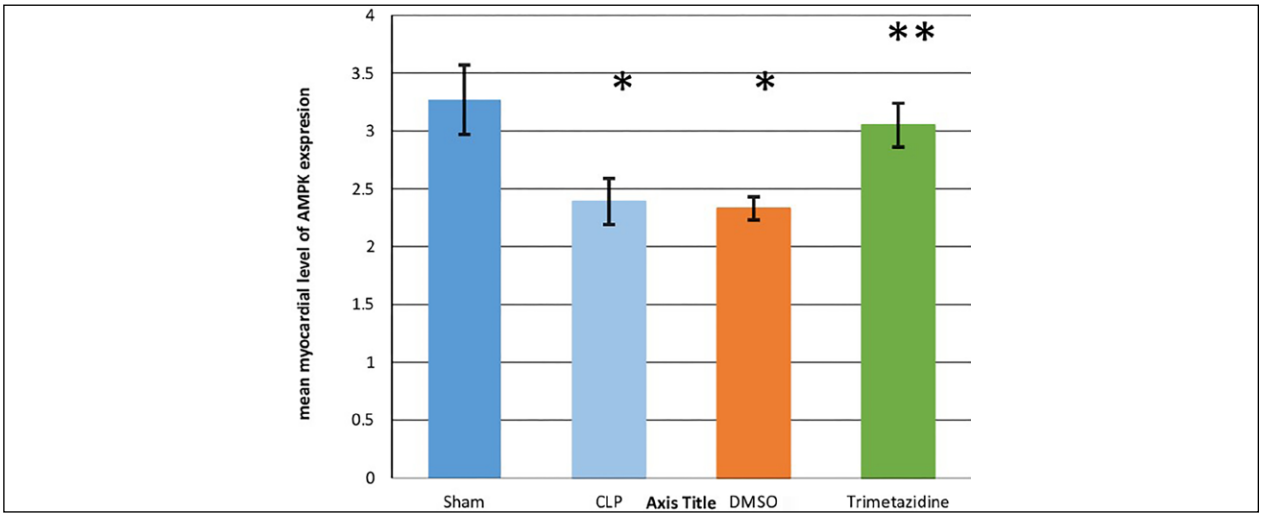

Fig. 9. Mean myocardial level of AMPK expression in the 4 experimental group 24 hours after sepsis. Data are expressed as mean ± SEM.
*: significant difference in CLP & DMSO as compare with the sham group; **: significant difference in pretreated group as compare with CLP group.

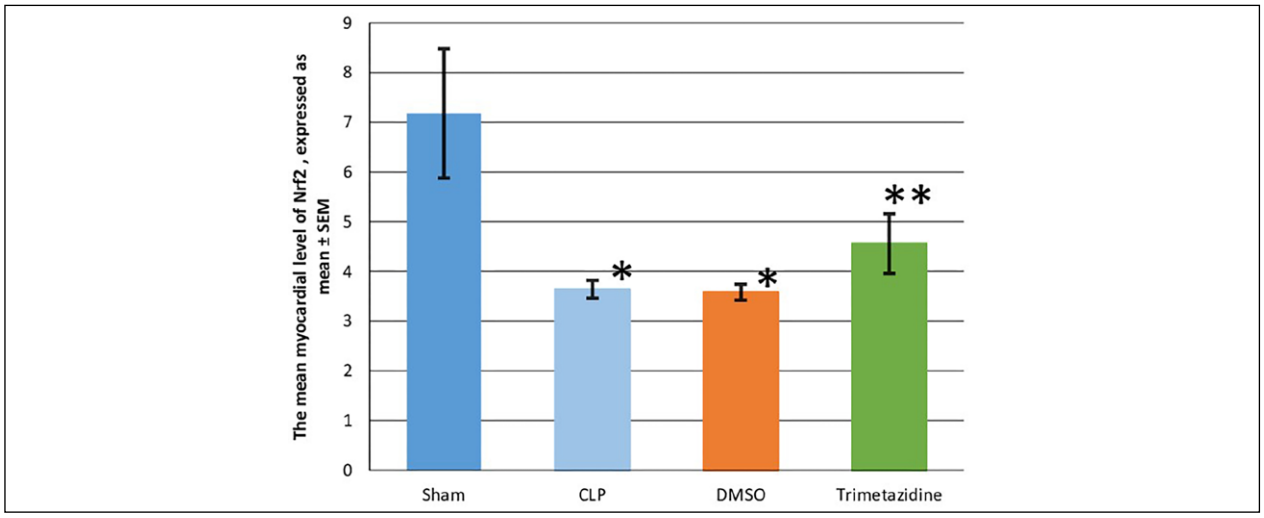

Fig. 10. Mean myocardial level of Nrf2 expression in 4 experimental groups 24 hours after sepsis. Data are expressed as mean ± SEM.
*: significant difference in CLP & DMSO as compare with the sham group; **: significant difference in pretreated group as compare with CLP group.

EFFECT OF TRIMETAZIDINE ON MRNA EXPRESSION OF AMPK-NRF2

Quantitative real-time PCR demonstrated a significant decrement in mRNA expression of AMPK-Nrf2 gene in CLP & DMSO groups when compared with the sham group ($p<0.05$). In comparison to the CLP & DMSO groups, the trimetazidine group had markedly increased levels of AMPK-Nrf2 ($p<0.05$) (Fig. 9-10).

HISTOPATHOTOGICAL FINDINGS

Data showed that CLP caused a significant tissue damage which was represented as scores from 0–4 and characterize a Sham group showing normal cardiomyocyte; CLP& DMSO groups, score 4, show necrotic cardiomyocyte. Trimetazidine group, score 2 show reduction in the tissue damage by reducing the necrosis in the cardiomyocyte.

SHAM GROUP

All animals in this group had normal histopathological findings (Fig.11A)

CECAL LIGATION AND PUNCTURE (CLP) GROUP

Score 4 damaged cardiac tissue (myocardial tissue sections of mice in the CLP group: showed congested blood vessels (black arrow) & extravasation of blood cells (red arrow), H & E, 10X) (Fig.11B).

DMSO GROUP

Score 4 damaged cardiac (tissue myocardial tissue sections of mice in the vehicle DMSO group: showed congested blood vessels (black arrow) & extravasation of blood cells (red arrow), H & E, 10X) (Fig.11C).

TRIMETAZIDINE GROUP

Trimetazidine group histological changes arranged from mild to moderate changes with a different number of mice (myocardial tissue sections of mice in the trimetazidine group: showed, interstitial oedema and focal necrosis (Fig.11D).

DISCUSSION

Sepsis is a critical condition-involving malfunction of organs due to an imbalanced immune response to infection, and it stands as a leading contributor to mortality among hospitalized individuals [17]. Moreover, sepsis is recognized as the foremost factor behind fatalities in intensive care units. Among the significant complications associated with sepsis is myocardial dysfunction, often referred to as sepsis-induced cardiomyopathy or cardiotoxicity, which substantially amplifies the mortality rate [18]. The current study focused on evaluating the prophylactic effects of trimetazidine in order to minimize the cardiotoxicity during polymicrobial sepsis in mice model which was done by cecal we showed that TNF-α, TNFαR, IL-1B, caspase-11, HO-1 MPO, F2-isoprostane levels was significantly elevated in the CLP and DMSO groups as compared with the sham group. This study is compatible with that obtained by Secher and others have highlighted that the TNF signaling pathway plays a central role in activating innate immunity in response to a variety of pathogens. In a polymicrobial sepsis model, evidence suggests a significant impact of TNF-R1 and R2 activation in the disruption of immune responses and the resultant mortality associated with sepsis [17]. This study agrees with a previous study which show that the elevation of TNFα and IL-1β level during the

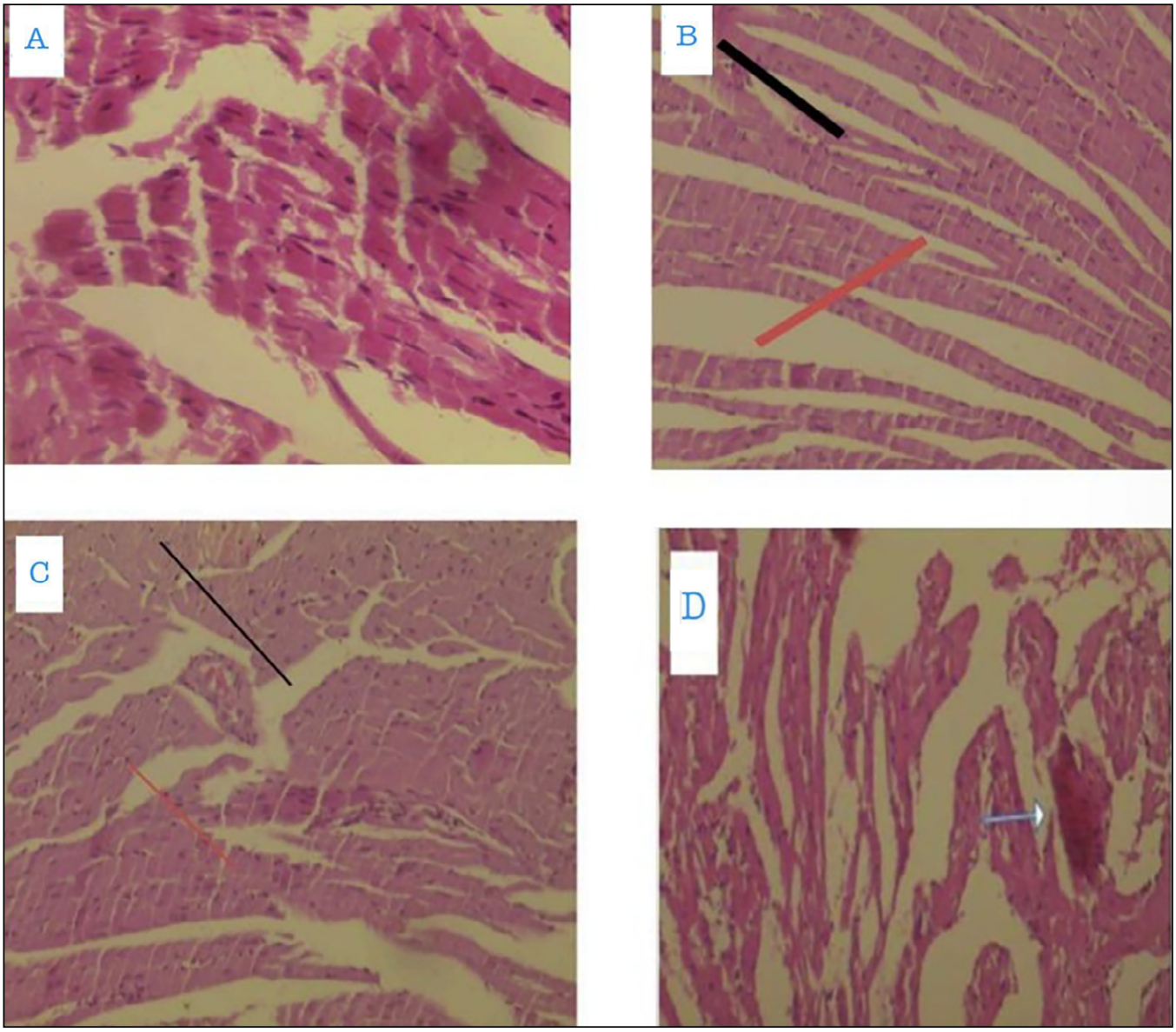

Fig. 11. Myocardial tissue sections of mice: (A) Sham group; (B) CLP group; (C) DMSO group; (D) Trimetazidine group. (H & E, 10X).

inflammatory phase of polymicrobial sepsis can be related to the microbial products activation of inflammasome which in turn will convert the inactive form of IL-1 β converting enzyme (ICE) into the active form that latter one will transform the precursor (pro- IL-1β) into the biologically active form (IL-1β) [19]. The present study reveals that there is a significant decrease in heart level of (IL-1β, TNFα) for trimetazidine pretreated group as compared to control group [20]. Trimetazidine decreased the expression of pro-inflammatory cytokines in cardiac and peritoneal macrophages stimulated by LPS. Trimetazidine-treated macrophage reduced apoptosis in cardiomyocyte that induced by LPS. The anti-apoptosis actions of trimetazidine caused by reduction in pro-inflammatory cytokines, mainly because of normalizing the sirtuins 1 (Sirt1)/ AMPK/Nrf2/ HO-1 and Sirt1/PPARα pathways in macrophages. Cytokine release was also controlled by ROS that were alleviated by trimetazidine through activation of the Sirt1/ AMPK/PPARα [21]. The current investigation demonstrates a substantial reduction in the heart's TNFαR1 levels within the trimetazidine pretreated group, when contrasted with the control group. As far as our current understanding goes, there exists a lack of available data concerning the influence of trimetazidine on TNFαR1 levels in cases of cardiac injury induced by endotoxins. This outcome is likely linked to the antioxidative properties of trimetazidine.

THE EFFEC OF SEPSIS ON CASPASE -11

Study reveals that there is a significant decrease in heart level of caspase- 11 for trimetazidine pretreated group as compared to control group. These findings imply that trimetazidine performs a critical role against cardiac damage. This protection mechanism is mainly due to its anti-inflammatory action by highly protein expression of AMPK.

These data suggest that pretreatment with trimetazidine may decrease apoptosis in the cardiomyocyte. Additionally, trimetazidine may potentiated expression of protein caused to ketogenesis through the activation of AMPK/PPARα signaling pathways [22].

THE EFFECT OF SEPSIS ON MYELOPEROXIDASE

The current investigation reveals that the administration of trimetazidine results in a noteworthy decrease in the levels of MPO within the group treated with trimetazidine, in comparison to the control group. This outcome aligns with findings from prior research suggest that trimetazidine acts main role in decreasing expression of MPO in rat lungs of silica-treated. This effect could potentially be achieved by inhibiting the overproduction of lactate induced by anaerobic glycolysis. Furthermore, the regulation of oxidative stress might contribute to the enhancement of protective effects exerted by trimetazidine [23, 24].

THE EFFECT OF SEPSIS ON THE OXIDATIVE STRESS BIOMARKERS HEME OXYGENASE-1 &F2-ISOPROSTANE

The present study finds out that trimetazidine causes a significant lower tissue level of HO-1 in trimetazidine treated group as compared with the control group. Trimetazidine reduced cardiomyocyte apoptosis and oxidative stress through activation of Nrf2/HO-1 pathway and inhibition of NF- B signaling pathway [23]. The present study finds out that trimetazidine causes a significant lower level of F2- isoprostane in trimetazidine treated group as compared with the control group. data suggested that trimetazidine highly reduced the serum levels of oxidative stress marker F2-isoprostane in patients with stable refractory angina [25].

THE EFFECT OF CLP ON CARDIAC TROPONIN-I

The present study revealed a noteworthy increase in the serum cardiac troponin levels within the CLP and DMSO groups when compared to the sham group. This outcome aligns with the results of a prior study conducted on rabbits to assess the impact of CLP-induced sepsis on cardiac troponin-I levels, where a substantial rise in cardiac troponin-I was detected in the experimental group compared to the control group of rabbits [26]. In this study, trimetazidine exhibited a significant reduction in the serum levels of cardiac troponin-I compared to the control group, indicating the preservation of heart function. This outcome aligns with [7], as their study also indicated a noteworthy decrease in cardiac troponin-I levels within the trimetazidine-treated group Trimetazidine has cytoprotective effect and protected the mitochondria against pressure overload and increased the ATP supply in cardiomyocytes [11].

EFFECT OF ON MRNA EXPRESSION OF AMPK-Nrf2

Our study demonstrated that the mRNA expression of AMPK-Nrf2 was significantly lower in the CLP and DMSO groups as compared with the sham group. This study agrees with a previous study, where they found that AMPK can function as a pivotal upstream target in Nrf2-related processes. Studies suggest that the activation of AMPK can alleviate both inflammation and redox imbalance through the Nrf2 signaling pathway, as demonstrated by Park et al. [27]. In the study conducted by previous study it was proposed that trimetazidine effectively mitigates myocardial impairment induced by CLP in mice [20]. This effect was achieved by enhancing the migration of neutrophils to cardiac tissue through a mechanism dependent on AMPK/Nrf2/CXCR2 signaling. Another independent study also suggested that trimetazidine could potentially reduce cell apoptosis in cardiac tissue [28]. These cardioprotective effects of trimetazidine may related to its anti-inflammatory and anti-oxidative action of AMPK & Nrf2 pathways Nrf2 controls antioxidant genes, leading to elimination of ROS and reduced inflammation [29].

EFFECTS ON MYOCARDIAL HISTOPATHOLOGY

In the present study, the group treated with trimetazidine exhibited a notable decrease in the extent of cardiac tissue injury. When compared with the CLP and DMSO groups the trimetazidine group showed moderate architecture with less degree of histopathological changes such as a moderate degree of inflammation and necrotic area [29]. The current study shows that pretreatment of mice exposed to CLP with trimetazidine improved heart damage suggesting that trimetazidine would have a protective impact against endotoxic cardiac injury [29]. The cardioprotective effects of trimetazidine are associated with its ability to counteract inflammation and oxidative stress through the activation of AMPK and Nrf2 pathways. Nrf2 is responsible for regulating genes involved in antioxidant responses, resulting in the clearance of reactive oxygen species (ROS) and a subsequent reduction in inflammation [20, 29].

CONCLUSIONS

The present study adds to the growing body of research that trimetazidine, has potential ameliorative impact on the mice that were subjected to CLP through its role as anti-inflammatory, antioxidant and anti-apoptotic effects.

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This study was performed in accordance with the recommendation of the Guide and Use of Laboratory animals' association for Laboratory animal science, Kufa University. All animals' considerations and conventions were approved by the Animal Care Committee. All mice used in this study were sacrificed were under xylazine and ketamine mixture anesthesia.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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RECEIVED: 01.11.2023
ACCEPTED: 04.07.2024