Tetramethylperazine alleviates sepsis-induced myocardial injury in mice by suppression NOX2-ERK1/2 signaling pathway


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ABSTRACT

Comprehensive epidemiological data on the global burden of sepsis are lacking despite its high associated mortality. The objective of this study is to examine the effectiveness of Tetramethylperazine (TMP) in attenuating myocardial injury during sepsis through signaling pathway of NOX2-ERK1/2. The resulted data showed that TMP improved cardiac function following CPL through %FS was significantly higher at 3 days after sepsis in TMP treated mice than CPL control and vehicle treated mice(45.0 ± 2.1% TMP, versus 22.1 ± 1.3CPL control<0.05). Moreover, TMP have effort in reduced cTn-I expression after sepsis. TMP neutralization of chemokine (MCP-1) and subsequently, reduced the infiltration of accumulation of monocytes and macrophages in myocardium following sepsis.ERK1/2 and NOX2 were significant down-regulation following TMP treatment. In conclusion, over expression of pro-inflammatory mediators following sepsis are suppressed LV function with upregulation of Nox2 protein and ERK1/2. While, the administration of TMP attenuated chemokine and cytokines through down-regulation of ERK1/2 activation singling pathway leading to improved left ventricular function.

Keywords: Sepsis; Pro-inflammatory mediators; Tetramethylperazine; myocardial injury; NOX2-ERK1/2

INTRODUCTION

Comprehensive epidemiological data on the global burden of sepsis are lacking in spite of its high associated mortality. Data obtained from high-income countries suggests that 31.5 million cases of sepsis and 19.4 million cases of severe sepsis occur globally each year, with potentially 5.3 million deaths annually (1). The major contributed factor of mortality and morbidity in septic patients is the myocardial dysfunction (2). In spite of the exact mechanisms which lead to myocardial dysfunction during sepsis are not fully understood, it was found that the cardiac dysfunction caused by the increase production of pro-inflammatory cytokines in the
heart, like tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 (3). Cardiac dysfunctions that occur in severe sepsis are characterized by impaired contractility due to impaired β-adrenergic signaling (4), diastolic dysfunction, and reduced ejection fraction (EF) (5). The mortality rate of septic patients with either systolic or diastolic dysfunction or both are higher than that in those without diastolic or systolic dysfunction (6). Impaired metabolism and reduced energy production in cardiomyocyte is occur because of cardiac dysfunction. The source of ATP production in the heart is primarily via fatty acid and glucose oxidation which are dropped in experimental models of sepsis (7) leads to accumulation of intracellular lipid and this result from impaired fatty acid oxidation and conversion of non-oxidized fatty acids into triglycerides (8). The major pathological changes occur in myocardial dysfunction during sepsis include myocardial infiltration by immune cells (specially Neutrophils and macrophages), subendocardium bleeding, interstitial and intracellular edema, endothelial cell edema, deposited of fibrin in the microcirculatory, also focal dissolution of myofibrillar, necrosis of cardiomyocytes, fibrosis of interstitial (9). Activation of the MAPK pathways can mediate by ROS (10). ROS production are induced by many cellular stimuli that in parallel can activate MAPK pathways in multiple cell types, after cell stimulation with cellular stimuli MAPK activation are blocked by antioxidants that prevent the accumulation ROS (11), that indicate involvement of ROS in activation of MAPK pathways. The mechanism(s) of the activation of MAPK pathways by ROS is not well defined. The oxidative modification of signaling proteins by ROS may be one of the plausible mechanisms for the activation of MAPK pathways. Because ROS can alter protein structure and function by modifying critical amino acid residues of proteins. (12). Also, it found that induced sustained activation of ERK pathway by glutamate-induced oxidative stress through a mechanism that involved degradation of MKP-1 (MKP-1 that maintain the pathway in an inactive state) (13). Tetramethylperazine (Rhizome Chuanxiong), is a Chinese medicine plant, that extract from Rhizome Chuanxiong and belongs to the amide alkaloids. Current research shows that TMP has anti-coagulative and antiplatelet aggregation functions because it can activate blood stasis, promote micro-circulation (14), it also shows anti-apoptotic effect in rabbit ischemic spinal cord and hydrogen peroxide (H2O2)-induced pheochromocytoma cells (PC12). A study using rabbits show that TMP can for fend articular cartilage and Chondrocyte from deterioration and apoptosis (12). It is used in the protection and treatment of ischemic diseases of vital organs such as the heart, kidneys and brain (11). Newly studies show that TMP inhibits inflammatory responses and is used in the treatment of biliary obstruction, burns, and other causes of myocardial injury. TMP can be effectively reduced the mortality rate of septic rats, protect cardiac function and relieve heart damage from inflammatory cytokines. The important of TMP are come from its vasodilating, free radical-scavenging, anti-inflammatory, anticoagulant and microcirculatory effects (17). TMP can improve the cardiac function; increase the EF in septic rats, and this lead to reduce the mortality rate. Accumulating evidence also shows that TMP helps maintain normal neuronal functions by preventing hypoxic and excitotoxicity cell damage in Hippocampal neurons (17) by scavenging free radicals, down regulating the production of nitric oxide and stimulating neuroprotective and anti-inflammatory processes after transient focal cerebral ischemia (18). The hypothesis of this study is to Examine the effectiveness of Tetramethylperazine in attenuating myocardial injury during sepsis through signaling pathway of NOX2-ERK1/2.
METHODS

Subjects and ethics

All study procedures comply with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Experimental Protocol

Mice were assigned to one of the following experimental groups (n = 8 in each group): sham group, vehicle group (equal doses of normal saline were administered i.p.), CLP group, CLP + pretreated with 10 mg/kg Tetramethylperazine (TMP) (Lot. No. 20101102, purity 99.3%) synthesized by Shanghai Medicilon Inc. (Shanghai, China) dissolved in saline were given (i.p.) at 1/2 h before sepsis. All treatments were performed in the morning and followed for survival for 72 hours. After analysis of cardiac function, the heart tissue and blood were collected and prepared for analysis.

Collection of samples

The blood was drawn using direct needle puncture of the heart. For plasma collection heparin was used as anticoagulant, the samples were stored at 4°C, centrifuged at 4700 × g for 10 min at 4°C, and the plasma was collected and stored at −20°C until used for further analyses, for plasma collection. For heart collection, a thoracic operation was performed; the heart of the mice was excised. Tissues samples of mice were cut into two parts: half of the samples were snap-frozen until use. The remaining samples were fixed for histological analysis.

Echocardiography

Transthoracic echocardiography was performed as described previously with a FFsonic 8900 (Fukuda Denshi) with a 10-MHz phased-array transducer at three days after surgery. The mouse is injected intraperitoneally with ketamine (100 mg/kg). Heart rates are monitored and generally maintained at 400–500 beats per minute and the chest hair is shaved. ECG needle leads are connected to the limbs for electrocardiogram gating. The mouse is then placed on a warm pad to keep the body temperature around 37°C. Warmed echo gel is placed on the shaved chest. The mouse heart is imaged with a 10 MHz linear transducer LV internal dimensions at end systole and end diastole (LVESD and LVEDD) were measured digitally on the M-mode tracings and averaged from 3 cardiac cycles. LV fractional shortening (%FS) was calculated as [(LVEDD − LVESD)/LVEDD] ×100.

ELISA

The samples of blood from mice were centrifuged (in 10000 RPM, for 10 minutes) and myocardial tissue was homogenized and treated in PBS containing 0.5% Triton X100 with a protease inhibitor cocktail. Commercial ELISA kits (R&D Systems) were utilized to quantify MCP-1, TNF-α, IL-1β and IL-6) in plasma and myocardial tissue, and plasma cardiac Troponin-I (cTn-I). Samples and standards were prepared according to manufacturer's instructions. Absorbance of standards and samples were determined spectro-photo metrically at 450 nm, by a microplate reader (Bio-Rad)
Western blot analysis

Hearts were homogenized with rotator machine with protease inhibitor cocktail 0.02 % (v/v), pH 7.4). Samples were centrifuged at 100,000 g for 10 min at 4°C, the supernatant was separate and divided into two parts. First part for determined the protein concentration after boiling for 10 min according the instruction of Bio Rad Bradford Assay Company [20], while, the second part for investigated the bands of ERK1/2 by Western blot as described previously according to the manufacturer’s instructions. Briefly, Proteins were transferred onto immunoblot membranes with polyvinylidene difluoride (Millipore, Chemicon International, MA). All membranes were blocked for 2 h with 5% BSA in Tris-buffered saline + 0.1% Tween (TBS-T), and incubated at 4°C overnight with the monoclonal antibody 48 (1/250 dilution) for NOX2 and primary antibodies of phospho-ERK1/2 (1:1000), β-acting (1:2000; Biotechnology), after washing membranes four times for 15 min with TBS-T, incubated with horseradish peroxidase-labeled secondary goat anti-rabbit (1:2000; Santa Cruz) for 1-hour. The membranes were second time washed four times for 15 min each in TBS-T, enhanced Chemiluminescence used to developed membranes (plygen Company, China). Finally, developed membranes bands imported into Adobe Photoshop software and semi-quantitative was analysis by scanning densitometry through Image J 3.0 system.

Histological examination

The cardiac tissue samples were fixed in 4% par formaldehyde for 24 h, as described previously [000]. Briefly, sections 5μm in thickness were paraffin embedded according to the standard procedure. Then, the samples were stained with the hematoxylin and eosin (H&E). The degree of heart damage and photographs were obtained from each heart section (n = 3 sections per heart) under optical microscopy.

Statistical analysis

Statistics were performed with the SPSS statistics program (windows version 9.0). To evaluate whether observed differences were significant, paired or non-paired t tests were used when appropriate. A p value (two sided) of less than 0.05 was significant.

RESULTS

TMP improved cardiac function following CPL

We determined whether TMP could improve cardiac function in mice following sepsis by using Echo. The measurements of LVEDD, LVESD, and %FS were similar between CPL control and vehicle treated mice. While, LVEDDs (mm) were significant (P<0.05) in TMP treated mice, and %FS was higher at 3 days after sepsis in TMP treated mice than CPL control and vehicle treated mice45.0 ± 2; with improved cardiac output 3.8 ± 0.3; P<0.05).

Table (1): Treatment with TMP improved LV function. Echocardiographic measures were obtained from a short-axis view at the level of the papillary muscle. Control
CPL and vehicle group a considerable reduction in the work of the left ventricle, including LVESDs, LVEDDs (mm), EF and CO, in rapprochement to sham mice.

<table>
<thead>
<tr>
<th>Echo Measures</th>
<th>Sham</th>
<th>Control CPL</th>
<th>Vehicle</th>
<th>TMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>595 ± 4</td>
<td>411 ± 2</td>
<td>422 ± 2</td>
<td>496 ± 5</td>
</tr>
<tr>
<td>LVESDs (mm)</td>
<td>4.2 ± 0.03</td>
<td>1.3 ± 0.04*</td>
<td>1.3 ± 0.15*</td>
<td>3.024±11*#</td>
</tr>
<tr>
<td>LVEDDs (mm)</td>
<td>5.4 ± 0.02</td>
<td>1.5 ± 0.21*</td>
<td>1.4 ± 0.11*</td>
<td>4.080±3*#</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>61± 1.3</td>
<td>22.1± 1.3*</td>
<td>21.1± 1.1*</td>
<td>45.0± 2.1*#</td>
</tr>
<tr>
<td>FS %</td>
<td>37± 2</td>
<td>20.1±2.4%*</td>
<td>21.9±1.3%*</td>
<td>26.4±0.5%*#</td>
</tr>
<tr>
<td>Cardiac output, ml/min</td>
<td>5.2± 1.2</td>
<td>2.3±0.6*</td>
<td>2.2±0.8*</td>
<td>3.8±0.3*#</td>
</tr>
</tbody>
</table>

Effective role of TMP in reducing myocardial injury

Moreover, our study investigated the myocardial cells injury by increased the level of plasma cardiac troponin-I (cTn-I). Interestingly, the level of cTn-I is associated with over expression of proinflammatory cytokines and Chemokines after sepsis. Moreover, cTn-I is related with elevated level of MCP-1 after sepsis that with released of the content of monocyte causing more cardiac injury, TMP has effort in reduced cTn-I expression after sepsis, figure (1).

Figure 1: Effort of TMP in reduced cTn-I expression after sepsis

Mean of plasma troponin I (pg/ml) in the five mice class. The results for plasma troponin are represented by (M±SE); number of animals in each division was eight: probability is less than 5% in compared to surgical control group: probability less than 5% in compare to control CPL and vehicle treatment: > 0.05 verses TMP treated mice.

TMP attenuate chemokine following 72h sepsis
Our previous lab study and others (10, 2), showed that the proinflammatory Chemokines (MCP-1) has been elevated after CPL and plays a substantial role in the accumulation of monocytes to the injured myocardium. In our study, we investigated the effects of TMP in neutralization of chemokine (MCP-1) and subsequently, reduced the infiltration of accumulation of monocytes and macrophages in myocardium following sepsis. In comparison to sham higher level of MCP-1 expression found in both control CPL and vehicle treated mice group, whereas the following 72h of sepsis the MCP-1 expressing within both the plasma and in the heart tissue markedly lower in treated mice with TMP following 72h of CLP, figure (2A, B).

![Graph A](image1.png)

![Graph B](image2.png)

**Figure (2):** MCP-1 was tested by SELISA technic after 3 day of CLP. In mice injected with TMP and AST the MCP-1 was decreased in myocardial tissue & plasma (A and B) respectively. The results are represented by (M±SE); number of animals in each division was eight: probability is less than 5% in compared to surgical control group: probability less than 5% in compare to control CPL and vehicle treatment: > 0.05 verses TMP treated mice.

**TMP reduced proinflammatory cytokines following CPL**

To examine the TMP effects on the cardiac tissue and systemic pro-inflammatory mediators during sepsis. After 72 hrs of sepsis the grade of pro-inflammatory IL-1β, IL-6 & TNF-α in myocardial tissue and plasma were measured by ELISA according to manufacture protocol. Comparison with sepsis and vehicle treated mice, TMP treated mice exhibit greater lowering the amount of all IL-1β, IL-6 and TNF-α expressed in both myocardium & plasma as in (Figure 3A and B).

![Graph](image3.png)
Figure (3): TMP reduced the level expression of proinflammatory cytokines in both myocardium figure (A) and plasma figure (B). The results are represented by (M±SE); number of animals in each division were eight: probability is less than 5% in compared to surgical control group; probability less than 5% in compare to control CPL and vehicle treatment: ¥P > 0.05 verses TMP treated mice.

**TMP decreased the level of myocardium ERK1/2**

In our study, we investigated the effects of TMP on expression of ERK1/2 following sepsis which analyzed by western blotting analysis. The result showed that ERK1/2 were upregulated following sepsis in myocardium in both vehicle and sepsis model. Significant down-regulation was observed following TMP treatment. Furthermore, the precise role that Nox2 plays in the mechanisms of myocardial ischemia remains unclear, the presented data showed increased NOX2 production after sepsis as shown in Figure 4, that corresponding with high expression of ERK1/2. Compared with the CPL, and vehicle group mice, the ERK1/2 were reduced after pretreatment with TMP; P<0.05.

![Western Blot Images](image)

Figure (4): Gel electrophoresis of Western blot products. ERK1/2 = 34-38kDa; NOX2=155 kDa; β-actin gene control= 42kDa

![Bar Graph](image)

Figure (3-5): Role of the NOx2 and ERK1/2 signaling pathway in CPL. Total protein was isolated from cardiac tissues and bands were determined by adobe Photoshop software and semi-quantitative was analysis by scanning densitometry through Image J 3.0 system. β-actin served as an internal control. The results are represented by (M±SE); number of animal in each division was eight: probability is less than 5% in compared to surgical control group; probability less than 5% in compare to control CPL and vehicle treatment > 0.05 verses TMP treated mice.

Histopathological changes after sepsis
Histological, myocardial tissue from CPL and vehicle mice after 72 hrs of sepsis period (Figure 6B and C) revealed a noteworthy cardiac injury and developed of a shrinking bar and polymorph nuclear leukocytes (PMN) infiltration besides interstitial edema and localized extravasations of red blood cells. While the histological features of the TMP treated mice showed mild architectural alterations (Figure 6D).

Figure (6): Sepsis effects to the myocardium tissue. Heart tissues were embedded and cut into sections (5µm thick). Sepsis causing cardiac depression was examined by H&E staining. Scale bar, 100 µm. Magnification: x40 and x100. Demonstrating extensive contraction band change (black arrows) with margination of poly-morph nuclear leukocytes (PMN) (white arrows) in CPL control and vehicle treated mice (A: Sham, B: CLP, C: Vehicle, D: TMP).

Figure (3-7): Zingarelli system show the degree of damage was considerably reduced in TMP and AST treated mice compared with the CPL mice after 72hrssepsis. The
results are represented by (M±SE); number of animals in each division were eight; probability is less than 5% in compared to surgical control group; probability less than 5% in compare to control CPL and vehicle treatment: > 0.05 verses TMP treated mice.

DISCUSSION

Sepsis is a systemic inflammatory response that may lead to cardiac dysfunction and manifested as reduced ejection fraction, impaired contractility, diastolic dysfunction which ultimately cause decreased cardiac output and heart failure (21). For a better understanding for the pathway of sepsis induced myocardial dysfunction, the present study investigated the role of TMP in the improvement of LV function following sepsis and possible pathway. According to our knowledge there were no data published previously discussed the relationship between NOX2/ERK1-2 pathway and effective role of TMP to improve cardiac function following sepsis induced by CLP model in mice. Our study showed that CLP and vehicles groups have significant decrease in heart rate, cardiac output, LVESD, LVEDD, ejection fraction and FS% as compared with sham group. These findings had been previously showed by (Yousif et al., 2017), which confirmed that septic mice experienced deterioration of left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP).

Histological, our results showed that mice myocardial tissue after 72 hr of CPL induced sepsis revealed a marked myocardial injury with development of contraction bands and polymorph nuclear leukocytes (PMN) infiltration in addition to interstitial edema and localized extravasations of red blood cells. Similarly, (22) showed that myocardial cells, following sepsis, exhibited granular degeneration, vacuolar degeneration, with myocardium cross-striations were blurred; and severe interstitial inflammation was present. In sepsis, cardiomyocytes participated in the inflammatory response by production of IL-6 and TNF-α (23). Although activated macrophages and cardiomyocytes secreted TNF-α, but the major source of cytokines in the heart is the cardiac fibroblast (24). Our study showed significant elevation in plasma and myocardial tissue levels of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) in CLP and vehicles groups as compared with sham group. The progression of cardiac dysfunction during sepsis may be related to over expression of IL-6, TNF-α, and IL-1β which has been confirmed by (25). Additionally, a previous study on rats showed that a rise in TNF-α and IL-1β levels in the CLP groups as compared with sham group (26). Furthermore, previous our lab studies reported that higher levels of pro-inflammatory cytokines and chemokine in both myocardial tissue and plasma attenuated cardiac contractility and associated with worse LV function performance through the cardiac function measurements by echocardiography (27). Activated macrophages produce proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, that are involved in the up-regulation of inflammatory responses (28). Additionally, using intravenous agents like IL-1β or TNF-α in animal studies has a similar process to that caused by sepsis lead to comorbidity and mortality (2), and this adverse effect of pro-inflammatory cytokines can be ameliorated by anti-inflammatory agents that antagonize the effects of these agents (29). Troponin I is a contractile protein consist from three isoforms, one of them is related to the cardiac fibers and the other are related to the skeletal muscle. Cardiac troponin I had no cross-reactivity with the other type of troponin and is a more sensitive and specific marker of cardiac damage than common serum enzymes (30). Our study showed a significant increase in cTn-I level in CLP septic group, suggested that the cTn-I may be related to express higher levels
of pro-inflammatory cytokines in the circulation. Moreover, cTn-I is related with elevated level of MCP-1 after sepsis that with released of the content of monocyte causing more cardiac injury. These finding were confirmed by (31). MCP-1 is a strong monocyte attractant, it responsible for the activation and migration of monocyte from blood stream to the locus of infection (32), exerted its effect by binding with G- protein receptors. Previous our lab studies reported that expression of chemokines like Monocyte Chemoattractant Protein-1 (MCP-1) in both plasma and myocardial tissue following sepsis mediate left ventricle dysfunction (20). Our results showed that higher levels expression chemokine like Monocyte Chemoattractant Protein-1 (MCP-1) in both myocardial tissue and plasma attenuated cardiac contractility and associated with worse LV function performance through the cardiac function measurements by echocardiography. NOX2 is a critical component in the phagocytic NADPH oxidase system and the ERK1/2 signaling pathway is a family of serine-threonine kinases, both are included with regulation of survival of cells and its proliferation (33). In end toxemic mice there are over expression of myocardial TNF-α, a major pro-inflammatory cytokine, that causes cardiac dysfunction, increases in NOX2 expression, superoxide generation and ERK1/2 phosphorylation (Wu et al., 2016). Sepsis leads to over expression of ERK1/2 (34). Our result showed that sepsis leads to excessive production of both NOX2 and ERK1/2 phosphorylation. Tetramethylperazine (TMP), is an active substance obtained from Chuanxiong rhizome, it has a wide range of therapeutic activity include reduction in the migration of proinflammatory cytokines and scavenging oxygen free radicals (35). Our study showed that pre-treat mice 1/2 h before sepsis with the TMP for 72 h lead to mild architectural alterations in the histological features. A study by (37) showed attenuation in the dissolved cardiomyocytes, distorted cardiac muscles, myocardial necrosis, the pretreated septic rats with TMP in a previous study by (31) showed that in myocardial cells were slight granular degeneration, myocardium cross-striations were clearly visible, and mild interstitial inflammation was present. According to our knowledge there were no published data discussed the relationship between NOX2/ERK1-2 pathway and effective role of TMP to improve cardiac function following sepsis by CLP model in mice. In our obtained results, we observed that pre-treatment with TMP resulted in significant improvement of echocardiographic LV function measurements. Our results showed that TMP treated mice exhibited greater reduction in the levels of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) in both myocardium and plasma, which are the same results that obtained by (38). Moreover (GUO et al., 2012) in their study demonstrated that pretreatment of septic rats with TMP can effectively reduce the mortality rate, relieves heart damage from inflammatory cytokines, and protects cardiac function. This indicated that TMP can decrease the TNF-α level and alleviate the inflammatory response of cardiomyocytes. Our result showed that pretreatment with of TMP causes reduction in the level of MCP-1.(36) mentioned in their study that treatment of mice with LPS injection causes an elevation in the serum levels of MCP-1 after 3 hr, but pretreatment of mice with AS-IV daily i.p. for 6 days followed by a single i.p. LPS injection caused significantly inhibited LPS-induced increases in serum MCP-1.Moreover (2) showed that TMP caused a reduction in the plasma level of (MCP-1) in rabbit aortas. Our study showed that TMP pretreated groups have a significant decrease in plasma level of cTn-I as compared with CLP and vehicle groups, these findings also agreed with the results obtained by (Wang et al., 2011). To understand the mechanistic pathway of TMP cardiac protection following sepsis, we tested the hypothesis that these agents improved cardiac function after sepsis through...
modulation of both NOX2 and ERK1/2 pathway. Our study demonstrated that pretreatment with TMP 1/2 h before sepsis significantly decreased NOX2 expression levels and ERK1/2 phosphorylation compared with CPL model mice. Similarly, (22) confirmed our results in their study by using hydroxyl methyl-3, 5, 6-trimethylperazine (HTMP) which is an active TMP metabolite, that has a longer half-life but the same beneficial effects of TMP. When using HTMP with carnitine esters in a one molecule showed that this new molecule exhibited a neuroprotective effect on experimental ischemic stroke, that can be attributed to reduce inflammatory responses and NOX2 derived oxidative stress. Furthermore, other study showed that TMP can inhibit AngII-induced proliferation and ET-1 activity, partially by interfering with the ERK pathway via attenuation of AngII and a consequent reduction of NAD(P)H oxidase-induced ROS generation(38). Interestingly, the analysis of western blot bands showed that significant correlation between NOX2 expression and ERK1/2 levels. Additionally, there were statistically no significant differences in ERK1/2 proteins expression levels between the different doses of TMP. Taking together, the above findings we can suggest that modulation in expression of NOX2/ERK1/2 signaling by both TMP may be the underlying mechanism which attenuates myocardial injury following sepsis.

CONCLUSION

Over expression of pro-inflammatory mediators following sepsis are suppressed LV function with upregulation of Nox2 protein and ERK1/2. While, the administration of TMP attenuated chemokine and cytokines through down-regulation of ERK1/2 activation singling pathway leading to improved left ventricular function.

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