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# Cardioprotective effects of irbesartan in polymicrobial sepsis

## The role of the p38MAPK/NF-κB signaling pathway

Sepsis is a systemic inflammatory reaction results from bacterial infection and is considered a main cause of death in critically ill patients [1, 2]. Myocardial dysfunction is one of the major signs of adverse outcomes in septic patients. It is usually correlated with decreased cardiac contractility, diastolic impairment, and cardiac injury, leading to a hypotensive condition. Approximately one fourth of patients with sepsis have cardiovascular complications, associated with elevated mortality rates of up to 70% [2–4]. Endotoxemia may decrease cardiac work via an increased expression level of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6. These cytokines act as cardiodepressant proinflammatory mediators [5], resulting in cardiac contractile dysfunction [6], cardiac hypertrophy, and heart failure [7, 8]. Furthermore, an increased cardiac troponin I (cTn-I) level during endotoxemia will decrease myofilament calcium responsiveness to a large extent and subsequently impairment of cardiac contractile function will occur [9–11]. We proposed that irbesartan plays a role in attenuation of cardiac depression during polymicrobial sepsis via decreased expression of the phospho-p38MAPK/nuclear factor (NF)-κB signaling pathway.

### Materials and methods

#### Experimental animals

A total of 32 adult male Swiss albino mice aged 8–12 weeks, weighing 20–30 g, were obtained from the College of Science, Babylon University and housed in the animal house of the College of Science of Kufa University. They were kept in cages under a 12 h light: 12 h dark cycle, with room temperature kept at 25 °C and humidity at 60–65%, with free access to food and water.

#### Study design

Mice were assigned randomly to one of the following groups ( $n = 8$  in each group): control group (cecal ligation and puncture [CLP]), sham group (negative control), irbesartan-pretreated group (3 mg/kg of irbesartan 1 h prior to CLP), and vehicle (PBS)-pretreated group.

#### CLP procedure

In the present study, mice were selected to induce polymicrobial sepsis in a model based on previous studies [12–14]. In brief, polymicrobial sepsis was induced by a double-puncture technique using 20-gauge needles. Mice were anesthetized using ketamine/xylazine solution [15]. Laparotomy was performed via a 1.5-cm midline incision and the cecum was exposed. The cecum was ligated just below the ileocecal valve and punctured; it was

then placed back in its anatomical position. The abdomen was sutured, using a 5.0 surgical suture (Ethicon, Norderstedt, Germany), and 1 ml of Ringer's solution was given s.c. for resuscitation. Mice were monitored for signs of disease every 4 h for 24 h. Sham-operated mice (anesthesia and laparotomy) served as the surgical control group.

#### Hemodynamic measurements

We assessed cardiac functions as described previously [16–18]. Briefly, mice were anesthetized intraperitoneally with ketamine at a dose of 50 mg/kg after CLP. Animals were placed supine on a heating blanket and body temperature was maintained at 37 °C ± 0.5 °C. The external right carotid artery was exposed, and a micro-tipped transducer catheter (1.4 F; Millar Instrument Inc., Houston, TX) was placed into the artery and then advanced into the left ventricle (LV). The other end of the catheter was connected to an electrostatic chart recorder (model ES 2000, Gould, Cleveland, Ohio) and pressure-volume loops were recorded to measure the maximum rate of change in ventricular pressure and ejection fraction by using an MPVS-400 system with the aid of PVAN software (Conductance Technologies, San Antonio, Tex., and Millar, Houston, Tex., respectively). Heart rates, LV end-diastolic pressure (LVEDP), and LV systolic pressure (LVSP) measurements were recorded.

**Table 1** Effect of irbesartan pretreatment on hemodynamic status of mice 24h after CLP<sup>a</sup>

Groups	Sham	CLP	Vehicle	Irbesartan
<i>Parameters</i>				
LVEDP (mm Hg)	3.2 ± 1.2	7.8 ± 1.4*	7.9 ± 1.2*	4.8 ± 1.3**
Ejection fraction (%)	65.1 ± 2	31.8 ± 3*	30.8 ± 1.2*	40.4 ± 1.1**
LVSP (mm Hg)	124.1 ± 1.3	54.2 ± 1.6*	54.7 ± 1.4*	82.5 ± 3.2**
Cardiac output (ml/min)	5.5 ± 1.2	3.2 ± 2.5*	3.1 ± 1.3*	3.4 ± 1.9**

\**p* < 0.05 vs. corresponding sham group, \*\**p* < 0.05 vs. untreated group

CLP cecal ligation and puncture, LVEDP left ventricular end-diastolic pressure, LVSP left ventricular systolic pressure

<sup>a</sup>Data are expressed as mean ± standard error, *n* = 8 in each group

## ELISA analysis

The blood samples of mice were centrifuged (10,000 rpm for 10 min) and myocardial tissue was homogenized and treated in PBS containing 0.5% Triton X100 with a protease inhibitor cocktail. Commercial ELISA kits (Bosterbio Corp., Pleasanton, CA) were utilized to quantify monocyte chemoattractant protein (MCP)-1, TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 as well as plasma cTn-I levels. Samples and standards were prepared according to the manufacturer's instructions. Absorbance values of standards and samples were determined spectrophotometrically at 450 nm, using a microplate reader (Bio-Rad Laboratories, Hercules, California, United States). The data obtained were plotted against the linear portion of a standard curve [19].

## Western blot

Myocytes of cardiac tissue were harvested with ice-cold PBS and centrifuged at 13,000 g for 3 min at 4 °C. Nuclear and cytosolic extracts were prepared using a Nuclear and Cytoplasmic Protein Extraction Kit (Beyotime Institute of Biotechnology, Jiangsu, China) according to the manufacturer's instructions. Protein concentrations were measured using a bicinchoninic acid protein assay kit (Beyotime). Equal amounts of lysates (50  $\mu$ g) were separated on 10% SDS-PAGE. Proteins were transferred onto immunoblot polyvinylidene difluoride membranes (Chemicon International, Millipore, Billerica, Mass), and the membranes were blocked with 5% BSA in Tris-buffered saline with 0.1% Tween (TBS-T) for 2 h and incubated overnight

at 4 °C with the following primary antibodies; MAPK (1:1000), phospho-p38 (1:1000), p38 (1:1000), rabbit anti-mouse NF- $\kappa$ B (1:1000; Santa Cruz Biotechnology, Delaware Ave, Santa Cruz, CA),  $\beta$ -actin (1:2000; Santa Cruz Biotechnology). Blots were washed four times for 15 min each in TBS-T and incubated with horseradish peroxidase-labeled secondary goat anti-rabbit (1:2000; Santa Cruz Biotechnology) or rabbit anti-goat (1:2000; Santa Cruz Biotechnology) for 1 h. Blots were again washed four times for 15 min each in TBS-T. Finally, blots were developed using the enhanced chemiluminescence (Pplygen Co., PPLYGEN, Beijing, China) method.

## Statistical analysis

Statistical analysis of the data was performed using StatView software (Abacus Concepts, USA). Analysis of variance (ANOVA) with Fisher's post-hoc test was used to investigate differences between the mice, and differences were confirmed using the Mann-Whitney *U* test. Statistical significance was set at *p*  $\leq$  0.05.

## Results

### Effect of irbesartan pretreatment on LV function after CLP

LV function was assessed 24 h after CLP to investigate the effect of treatment with irbesartan on sepsis-induced myocardial dysfunction. The results in **Table 1** show that both the CLP and vehicle groups had significantly (*p* < 0.05) attenuated LV function with decreased ejection fraction, cardiac output, and

LVSP and an increase in heart rate and LVEDP as compared with the sham group. Further, the irbesartan-treated group had improved LV function through increased ejection fraction, cardiac output, and LVSP as well as reduced heart rate and LVEDP.

### Effect of irbesartan pretreatment on plasma level of proinflammatory cytokines after CLP

At the end of the experiment (24 h after CLP), the levels of plasma proinflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , and IL-6) were increased in the CLP and vehicle groups compared with the irbesartan treatment group.

The changes in plasma proinflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6) levels are shown in **Fig. 1**.

### Effect of irbesartan pretreatment on the plasma level of MCP-1 after CLP

At the end of the experiment (24 h after CLP), the plasma MCP-1 level was increased in the CLP and vehicle groups compared with the irbesartan treatment group. The changes in the plasma MCP-1 level are shown in **Fig. 2**.

### Effect of irbesartan pretreatment on myocardial injury after CLP

The plasma level of cTn-I was significantly (*p* < 0.05) increased in the CLP and vehicle groups as compared with the sham group. The cTn-I level of the irbesartan-treated group was significantly (*p* < 0.05) lower than that of the CLP group. The changes in cTn-I level are presented in **Fig. 3**.

### Irbesartan pretreatment attenuates phosphorylation of p38MAPK/NF- $\kappa$ B in cardiomyocytes after CLP

Myocardial tissue homogenates were analyzed using the Western blot technique. The p38MAPK/NF- $\kappa$ B phosphorylation in myocardial cells was significantly (*p* < 0.05) increased in the CLP and vehi-

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**Cardioprotective effects of irbesartan in polymicrobial sepsis. The role of the p38MAPK/NF-κB signaling pathway****Abstract**

**Background.** Sepsis is a systemic inflammatory response usually correlated with multi-organ failure. Myocardial dysfunction is one of the adverse outcomes in septic patients and results in high mortality rates. The aim of this study was to investigate the impact of irbesartan in attenuation of cardiac depression during polymicrobial sepsis via decreased activation of the phospho-p38MAPK/nuclear factor (NF)-κB signaling pathway.

**Materials and methods.** A model of polymicrobial sepsis induced via cecal ligation and puncture (CLP) with 8- to 12-week-old albino mice was used. Mice were treated with i.p. irbesartan (3 mg/kg) 1 h before CLP. Using a micro-tipped transducer catheter,

the following hemodynamic parameters were evaluated after CLP: heart rate, ejection fraction, left ventricular (LV) end-diastolic pressure, LV systolic pressure, and cardiac output. Plasma levels of proinflammatory cytokines, including tumor necrosis factor (TNF)-alpha, interleukin (IL)-1 beta, IL-6, monocyte chemoattractant protein-1 (MCP-1), and cardiac troponin I (cTn-I), were measured via ELISA analysis. The degree of p38MAPK and NF-κB phosphorylation was assessed via Western blotting.

**Results.** Mice treated with irbesartan displayed improvement in LV function (ejection fraction:  $42.4 \pm 1.1\%$  vs.  $27.8 \pm 3\%$  in CLP mice). The attenuation of cardiac depression

in irbesartan-treated mice was associated with lower levels of MCP-1 in plasma and a reduction in the levels of TNF-alpha, IL-1beta, and IL-6. Furthermore, irbesartan-treated mice displayed lower expression levels of p38-MAPK and NF-κB phosphorylation.

**Conclusion.** Irbesartan can attenuate cardiac dysfunction during polymicrobial sepsis possibly via a reduction of proinflammatory cytokines through decreased activation of the p38MAPK/NF-κB pathways.

**Keywords**

Septicemia · Acute-phase reaction · Cytokines · Hemodynamics · Anti-hypertensive agents

**Kardioprotektive Wirkungen von Irbesartan bei polymikrobieller Sepsis. Bedeutung des p38MAPK/NF-κB-Signalwegs****Zusammenfassung**

**Hintergrund.** Die Sepsis stellt eine systemische entzündliche Reaktion dar, die gewöhnlich mit Multiorganversagen einhergeht. Myokardfunktionsstörungen sind eine der ungünstigen Folgen bei septischen Patienten und führen zu einer hohen Mortalitätsrate. Ziel der vorliegenden Studie war es, den Einfluss von Irbesartan auf die Abschwächung der Kreislaufdepression bei polymikrobieller Sepsis über eine verminderte Aktivierung des Signalwegs von Phospho-p38MAPK/Nuclear-Factor(NF)-κB zu untersuchen.

**Material und Methoden.** Es wurde ein Modell der polymikrobiellen Sepsis verwendet, bei dem die Sepsis über eine Ligatur und Punktur des Zoekums („cecal ligation and puncture“, CLP) bei 8–12 Wochen alten Albinomäusen induziert wurde. Die Mäuse

wurden i.p. mit Irbesartan (3 mg/kg) 1 h vor CLP behandelt. Unter Einsatz eines Mikrotip-Transducer-Katheters wurden die folgenden hämodynamischen Parameter nach CLP gemessen: Herzfrequenz, Ejektionsfraktion, linksventrikulärer (LV) enddiastolischer Druck, LV systolischer Druck und Herzzeitvolumen. Mittels ELISA-Test wurden die Plasmaspiegel proinflammatorischer Zytokine einschließlich Tumornekrosefaktor-alpha (TNF-α), Interleukin-1beta (IL-1β), IL-6, Monozytenchemoattraktives Protein-1 (MCP-1) und kardiales Troponin I (cTn-I) bestimmt. Der Grad der Phosphorylierung von p38MAPK und NF-κB wurde per Western-Blot-Test ermittelt.

**Ergebnisse.** Die mit Irbesartan behandelten Mäuse wiesen eine Verbesserung der LV-Funktion auf (Ejektionsfraktion:  $42,4 \pm 1,1\%$  vs.  $27,8 \pm 3\%$  bei CLP-Mäusen). Die

Abschwächung der Kreislaufdepression bei den mit Irbesartan behandelten Mäusen ging mit niedrigeren Plasmaspiegeln von MCP-1 und einer Senkung der Werte für TNF-α, IL-1β und IL-6 einher. Darüber hinaus zeigten die mit Irbesartan behandelten Mäuse eine geringere Expression der Phosphorylierung von p38-MAPK und NF-κB.

**Schlussfolgerung.** Irbesartan kann möglicherweise über eine Verminderung proinflammatorischer Zytokine durch geringere Aktivierung des p38MAPK/NF-κB-Signalwegs zu einer Abschwächung der kardialen Funktionsstörung bei polymikrobieller Sepsis führen.

**Schlüsselwörter**

Septikämie · Akute-Phase-Reaktion · Zytokine · Hämodynamik · Antihypertensiva

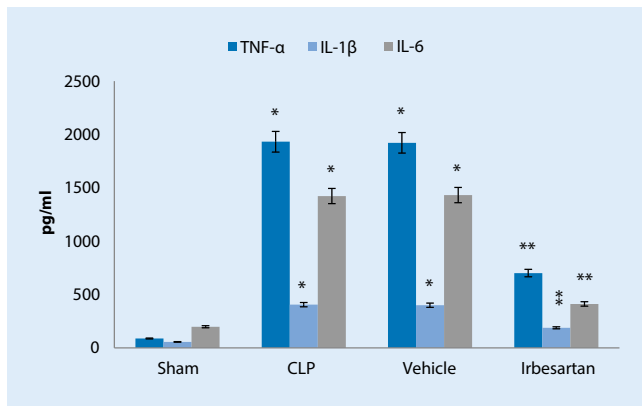
cle groups as compared with the sham group. The NF-κB phosphorylation in the irbesartan-treated group was significantly ( $p < 0.05$ ) lower than that of the CLP group: This indicates the involvement of NF-κB in the mechanistic action of irbesartan. The phosphorylated p38MAPK level of the irbesartan-treated group was significantly ( $p < 0.05$ ) lower than that of the CLP group: This indicates the involvement of p38MAPK in

the mechanistic action of irbesartan. The changes in p38MAPK and NF-κB level are presented in **Fig. 4**.

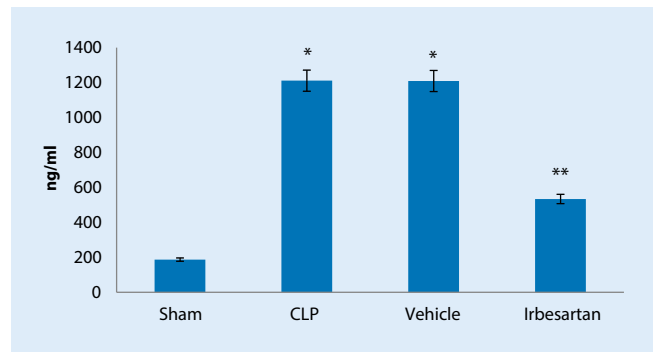
**Discussion**

During sepsis, the inflammatory responses mediate myocardial injury, including LV dysfunction and cardiac pathophysiological changes [20–22]. Previous studies reported that plasma

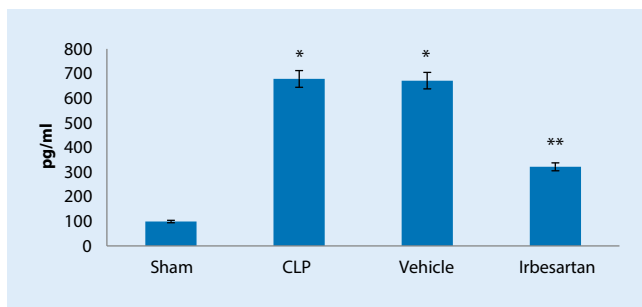
levels of inflammatory mediators (IL-1β, TNF-α, and IL-6) were higher following myocardial injury and sepsis [23–25]. Furthermore, another study confirmed in vivo increased MCP-1 levels in both plasma and myocardial tissue in a mouse model after sepsis [26]. To understand the pathway of sepsis in the context of endotoxemic cardiac depression, the present study investigated the role of irbesartan pretreatment in improving



**Fig. 1** ▲ Mean plasma proinflammatory cytokines (pg/ml) in the four experimental groups 24 h after CLP. Data are expressed as mean ± standard error; \* $p < 0.05$  vs. corresponding sham group; \*\* $p < 0.05$  vs. CLP group. CLP cecal ligation and puncture, IL interleukin, TNF tumor necrosis factor



**Fig. 2** ▲ Mean plasma MCP-1 level (ng/ml) in the four experimental groups 24 h after CLP. Data are expressed as mean ± standard error; \* $p < 0.05$  vs. corresponding sham group; \*\* $p < 0.05$  vs. CLP group. CLP cecal ligation and puncture



**Fig. 3** ▲ Mean plasma cTn-I (pg/ml) in the four experimental groups 24 h after CLP. Data are expressed as mean ± standard error; \* $p < 0.05$  vs. corresponding sham group; \*\* $p < 0.05$  vs. CLP group. CLP cecal ligation and puncture

cardiac function following sepsis. According to our knowledge, there are no published data discussing the relationship between the p38MAPK/NF- $\kappa$ B pathway and the effective role of irbesartan on improved cardiac function following sepsis in a CLP mouse model.

### Sepsis attenuated myocardial function via elevation of inflammatory mediators

A number of published studies have confirmed that myocardial dysfunction during sepsis is related to the expression of inflammatory mediators, including IL-6, TNF- $\alpha$ , and IL-1 $\beta$  [26, 27]. Furthermore, inflammatory cytokines have been up-regulated in myocardial dysfunction after acute injuries caused by sepsis, myocardial ischemia, and reperfusion [26, 28, 29]. Additionally, intravenous administration of either TNF- $\alpha$  or IL-1 $\beta$  in animal experiments can evoke a similar process

to that caused by sepsis leading to cardiac comorbidity and mortality [26]. The aforementioned adverse effects of proinflammatory cytokines can be ameliorated by antibodies that antagonize the effects of these molecules [29–31]. Other studies have demonstrated that TNF- $\alpha$  also plays an important role in septic myocardial dysfunction and that TNF- $\alpha$  is linked to the TLR4 activation pathway [30, 32]. In the present study, we demonstrated that sepsis increases the levels of inflammatory mediators (IL-1 $\beta$ , TNF- $\alpha$ , and IL-6) in both plasma and cardiac tissue of mice, and that it is associated with worse LV function performance as reflected in the hemodynamic measurements (heart rate, ejection fraction). Furthermore, these results are associated with increased levels of circulating cTn-I in mice exposed to CLP. Our data suggest that significantly higher levels of myocardial depressant proinflammatory cytokines in the heart directly attenuated cardiac contractility

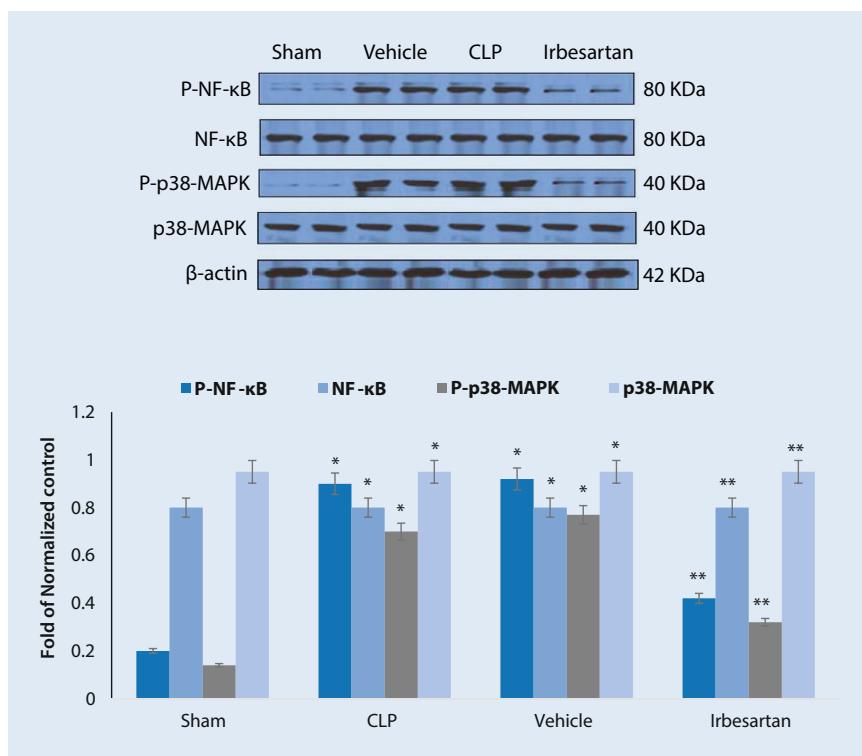
and induced myocardial injury. Taken together, these results contribute partly to the mechanism of exaggerated cardiac depression in an experimental sepsis mouse model. Interestingly, we observed that pre-treatment with irbesartan resulted in a greater reduction in cytokines with an improvement in LV function: Ejection fraction was improved ( $40.4 \pm 1.1$ ) in irbesartan-treated mice. Additionally, pretreatment with irbesartan improved other LV function parameters, such as LVESP ( $82.5 \pm 3.2$ ) and cardiac output ( $3.4 \pm 1.9$ ).

### Sepsis up-regulated myocardial MCP-1 expression level

Many studies have demonstrated that MCP-1 decreased the recruitment of neutrophils and reduced tissue injury in many animal models of sepsis-induced organ injury [33–35]. In the present study, we found that MCP-1 levels in plasma and cardiac tissue were significantly higher in the CLP group than in the sham group.

### Down-regulation of p38MAPK/NF- $\kappa$ B improved LV function

The intracellular downstream signaling pathway of TLR4 includes phosphorylation of p38MAPK and activation of NF- $\kappa$ B [10, 11, 36, 37]. In the present work, we investigated the mechanisms of action of irbesartan. Our findings suggest that irbesartan decreased cardiac injury in



**Fig. 4** ▲ Mean relative p38MAPK/NF-κB activity in the four experimental groups 24 h after CLP. Data are expressed as mean ± standard error; \* $p < 0.05$  vs. corresponding sham group; \*\* $p < 0.05$  vs. CLP group. CLP cecal ligation and puncture

the irbesartan-pretreated group through its ability to decrease both the degree of p38MAPK phosphorylation and NF-κB activation as compared with the CLP group, which showed an elevated level of p38MAPK phosphorylation and NF-κB activation.

## Conclusion

This study found that both p38MAPK phosphorylation and NF-κB activation are increased during sepsis and lead to attenuation of LV function. Additionally, it was found that both p38MAPK phosphorylation and NF-κB activation are closely related to increased plasma and tissue levels of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which leads to decreased LV function. This finding suggests that both p38MAPK phosphorylation and NF-κB activation could be biomarkers and novel targets for therapy in patients with cardiac complications during sepsis via improvement of LV function. These experimental results indicate that endogenous p38MAPK phosphorylation and NF-κB activation

mediate the expression of MCP-1, leading to increased levels of cTn-I and subsequently myocardial cell injury. Western blot analysis proved the low levels of both p38MAPK and NF-κB in irbesartan-pretreated mice compared with the sham or vehicle-treated groups. The effects of p38 MAPK or NF-κB inhibitors during sepsis remain to be further studied and tested.

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## Compliance with ethical guidelines

**Conflict of interest.** N.G. Yousif, N.R. Hadi, F. Al-Amran, and Q.A. Zigam declare that they have no competing interests.

All national guidelines on the care and use of laboratory animals have been followed and that the

necessary approval was obtained from the relevant authorities.

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## Fachnachrichten



### E-Health und Digitalisierung

#### Online-Befragung der TU München

Egal ob Online-Therapie bei Depressionen, Visite mit Tablet-Computer oder Kommunikation mit Parkinson-Patienten per Videosprechstunde: Digitalisierung in der Medizin ist in aller Munde. Doch was bedeutet das für Ärztinnen und Ärzte, die in Praxen oder Kliniken tätig sind? Wie stehen sie zu den Chancen und Herausforderungen der digitalen Medizin?

Eine Umfrage der AG Versorgungsforschung der Klinik für Unfallchirurgie am Klinikum rechts der Isar untersucht die Einstellung und Meinung von Medizinern zu diesem Thema. Die Befragung richtet sich an Ärztinnen und Ärzte aller Fachrichtungen und dauert fünf bis zehn Minuten. Sie umfasst Fragen zu bestehenden digitalen Angeboten, zu zukünftigen Entwicklungen, zur praktischen Machbarkeit und zur Akzeptanz. Die Beantwortung erfolgt anonym und kann an jedem Punkt der Befragung abgebrochen werden.

Die Studie berücksichtigt die geltenden Datenschutzrichtlinien und wurde von der Ethikkommission der Fakultät für Medizin der Technischen Universität München bewilligt.

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