

# Assessing the therapeutic effect of resveratrol in heart failure following blunt chest trauma and the potential role of endocan as a biomarker of inflammation using rats

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## ABSTRACT

**BACKGROUND:** The present study investigated the therapeutic effect of resveratrol on cardiac injury resulting from blunt chest trauma and the utility of endocan as a biomarker of the inflammation process using rats.

**METHODS:** The rats were randomly divided into the following four groups (n=7 in each group): a control group (no treatment or trauma); trauma-induced group (trauma group); resveratrol group (resveratrol 0.3 mg/kg administered via the intraperitoneal [i.p.] route group); and resveratrol + trauma group (resveratrol 0.3 mg/kg administered via the i.p. route 1 hour prior to the induction of trauma).

**RESULTS:** The immunoreactivity of tumor necrosis factor- $\alpha$  and inducible nitric oxide synthase in the trauma group was increased, whereas the reaction intensity in resveratrol + trauma group was decreased. The mean endocan values of the differed between the groups ( $p<0.001$ ). The mean endocan value in the resveratrol + trauma group was higher than that of the other groups.

**CONCLUSION:** Resveratrol exhibited anti-inflammatory and antioxidant effects in lung injury after blunt chest trauma and contributed favorably to the treatment process. We believe that there is a need for further studies on the clinical use of endocan as a biomarker of inflammation in cardiac injury after blunt chest trauma.

**Keywords:** Blunt chest trauma; cardiac injury; endocan; resveratrol.

## INTRODUCTION

Nutraceuticals are derived from foods and have pharmacological and therapeutic properties.<sup>[1]</sup> Resveratrol is a natural phenolic compound that has many beneficial effects on the human body. It is present in abundant amounts in grapes, peanuts, strawberries, and plums. Previous studies investigated the effects of resveratrol in various diseases.<sup>[2-4]</sup> One study reported that resveratrol exhibited antiatherogenic properties by decreasing the levels of prostaglandin E2 and plasminogen activator inhibitor-1.<sup>[3]</sup> Another study showed that resveratrol had anticancer properties, increasing vascular endothelial growth factor and levels of apoptosis regulator Bax.<sup>[5]</sup> Further research suggested that resveratrol regulated metabolism, glucose, and lipid levels and that it had positive effects on

chronic diseases, such as diabetes, obesity, and liver disease.<sup>[6]</sup> Studies have also examined the effects of resveratrol on cardiovascular diseases, especially atherosclerotic heart diseases and hypertension.<sup>[7,8]</sup> It was found that resveratrol protected cardiomyocytes from oxidative stress, limited inflammation associated with atherosclerosis by reducing prostaglandin E2 levels, and exhibited anti-inflammatory properties.<sup>[9]</sup> Further, it exerted a positive effect on hypertension by inducing vasodilatation and neovascularization.<sup>[5]</sup> However, there have been no studies till date that assess the effect of resveratrol on cardiac contusions caused by blunt chest trauma.

Blunt chest trauma can cause fatal complications, as it affects the organs that regulate vital functions, such as the heart and lungs. Rapid detection and treatment of the damage can be

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life-saving.<sup>[10,11]</sup> However, blunt chest trauma can be difficult to detect due to inadequate diagnostic methods and lack of a gold standard. The mortality rate after blunt chest trauma increases in the presence of heart failure.<sup>[12]</sup> For this reason, new methods and markers are needed for rapid diagnosis.

The endothelium is the largest organ in the body and plays a role in many pathological conditions in the vasculature. The main function of the endothelium is to provide an anticlotting surface and induce the release of vasoactive substances and various cytokines that facilitate the inflammatory process. Endocan, a protein synthesized from active vascular endothelial cells, exhibits anti-inflammatory properties by inhibiting leukocyte adhesion and migration.<sup>[13]</sup> Some previous studies found that high endocan levels were associated with various medical conditions, such as inflammation, cancer, sepsis, and obesity.<sup>[13–15]</sup> There are different results, even in limited numbers of sample groups.<sup>[16,17]</sup>

The present study used rats to investigate the therapeutic effect of resveratrol on cardiac injury resulting from blunt chest trauma, the association of serum levels of endocan with the inflammation process, and the utility of endocan as a biomarker of inflammation in cardiac disease.

## MATERIALS AND METHODS

The experimental protocol and all animal procedures were approved by the Experimental Ethics Committee.

### Animals and Experimental Protocol

All animals were provided by the Experimental Research Center. A total of 28 female Sprague-Dawley rats weighing 235–275 g were used in the experiments. They were kept under standard experimental laboratory conditions (temperature: 24°C; dark/light cycle: 12/12 hours; free access to food and water; relative humidity: 60%).

The rats were anesthetized with an intraperitoneal (i.p.) injection of ketamine hydrochloride (100 mg/kg) and xylazine (10 mg/kg) and allowed to breathe spontaneously during the procedure. The rats were randomly divided into four groups (n = 7 in each): a control group, trauma group (trauma only), resveratrol group (resveratrol treatment administered via the i.p. route), and resveratrol + trauma group (resveratrol treatment administered 1 hour prior to trauma). The resveratrol (Sigma Aldrich, Germany) dose was 0.3 mg/kg i.p.<sup>[4]</sup>

**Trauma model:** A platform was suspended on Teflon rails to reduce friction and facilitate energy transfer to the animal. An important feature of the model, a precordial protective shield (Plexiglas), was placed under the Lexon Platome in direct contact with the chest. This shield directs the energy of the pulse toward the side of the chest. The xiphoid field was clearly marked on each animal, and the shield was repeatedly

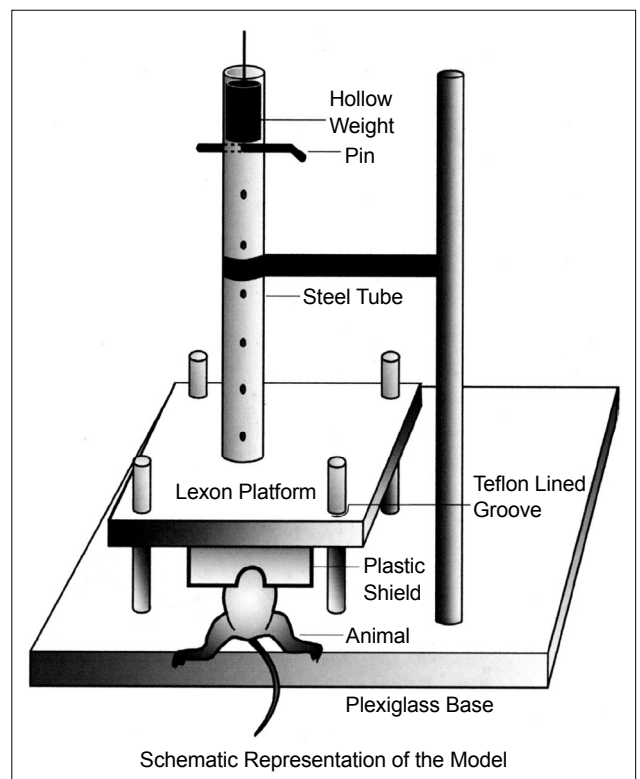
placed on the chest, without intervention by the neck or abdomen (Fig. 1).<sup>[18]</sup>

The anesthetized rats were fixed between the lower and upper platform, with their chests facing upward. Thoracic trauma was induced by placing a hollow aluminum cylinder weight (0.3 kg) through a vertical stainless steel tube on the Lexan platform adjacent to the chest.

After 24 hours, all the experimental rats were sacrificed with an i.p. injection of ketamine hydrochloride. Approximately 3 ml of blood samples were collected in tubes with cardiac puncture anticoagulant for biochemical analyses. The tubes containing the blood were left in the room for 30 minutes to clot. The sera were then centrifuged at 3000 g for 10 minutes at 4°C and were stored at –80°C until used in the analysis. After the surgical procedure, heart samples were collected for histopathological and immunohistochemical investigations.

## Histopathological Studies

Materials were prepared by appropriate methods and then preserved in 10% formaldehyde solution for histological



**Figure 1.** Schematic of the rat model of isolated bilateral pulmonary contusion. A hollow cylindrical weight held in place with a pin at a defined height was dropped through a steel tube onto a Lexon platform with an underlying precordial shield contacting the chest of an anesthetized rat. Teflon guides minimize fractional dissipation and maximize energy transfer to the animal. The precordial shield allowed the induction of bilateral pulmonary contusion but spared the mediastinum and associated structures. The severity of lung contusion was dependent on the impact force of the falling weight

examinations. Subsequently, the materials were routinely subjected to histological tissue sequencing procedures and blocked in paraffin. After cutting sections of 5 µm thickness from paraffin blocks, Crossman's triple staining method was used to examine the histological structures. The resulting preparations were photographed under a Nikon E600 research microscope containing a Nikon digital-sight imaging system.<sup>[19]</sup>

### Immunohistochemistry Procedure

In the 5 µm lung sections cut from paraffin blocks, the presence of tumor necrosis factor-α (TNF-α) and inducible nitric oxide synthase (iNOS) was examined by immunohistochemical methods using the streptavidin-biotin complex method.<sup>[20]</sup> In immunohistochemical staining, rabbit polyclonal TNF-α (Abcam, ab9739) and rabbit polyclonal iNOS (Abcam, ab3523) primary antibodies were used. The Histostain Plus rabbit primary (Zymed kit: 85-6743) kit was used as the secondary antibody. The sections were deparaffinized and then heated in a 700 watt microwave oven for proteolysis in a citrate buffer (pH: 6) solution. The tissues were then incubated in 3% hydrogen peroxide solution to prevent endogenous peroxidase activity. After washing with phosphate buffered saline (PBS), serum was instilled into the kit to prevent nonspecific protein binding in the sections. Primary antibodies with 1/200 (TNF-α) and 1/250 (iNOS) dilutions were then instilled into the sections and incubated at - 4°C overnight. Only PBS solution was instilled into the negative control group tissues. Following washing, the biotinylated secondary antibody was added to the sections and incubated with the streptavidin-HRP complex. In the last step, 3,3'-diaminobenzidine was used as a chromogen and the preparations were sealed with adhesive and counterstained with hematoxylin. In the immunohistochemical evaluations, values of 0 to 3 were assigned according to the level of staining: unstained (-), weak staining (+), moderate staining (++), and severe staining (+++).

### Biochemical Procedure

All the samples were allowed to dissolve at 2°C–8°C the day before the analyses were performed. Serum samples of endocan were measured using a rat ESM-I ELISA kit (Bioassay Technology Laboratory, Shanghai, China) in accordance with the manufacturer's protocol. Troponin I (TnI) was determined using a Rat TnI ELISA kit (E Lab science, Texas, U.S.A.), and N- terminal pro-brain natriuretic peptide (NT pro-BNP) was

determined using a Rat NT pro-BNP ELISA kit (E Lab science, Texas, U.S.A.) in accordance with the procedures specified by the manufacturer. TnI, NT pro-BNP, and endocan levels are given in ng/ml.

### Statistical Analysis

Data were analyzed using the SPSS 21.0 package software. The measurements obtained were expressed in median (minimum-maximum). For data with a normal distribution, an analysis of variance was performed. The Kruskal–Wallis test was conducted for data showing a non- normal distribution. The level of statistical significance was accepted at p<0.05.

## RESULTS

### Histopathological Results

The histopathological analysis revealed three main layers (endocardium, myocardium, and pericardium) in the heart tissue. Endocardium, a thin membrane covering the inside of the atrium and ventricles, was present at the innermost layer of the tissue. The middle layer was fairly thick and consisted of heart cells. On the outermost side, a thin membrane epicardium consisting of the visceral leaf of the pericardium was observed. Intercalated disc spaces and collateral connections between the cardiac cells were clearly visible.

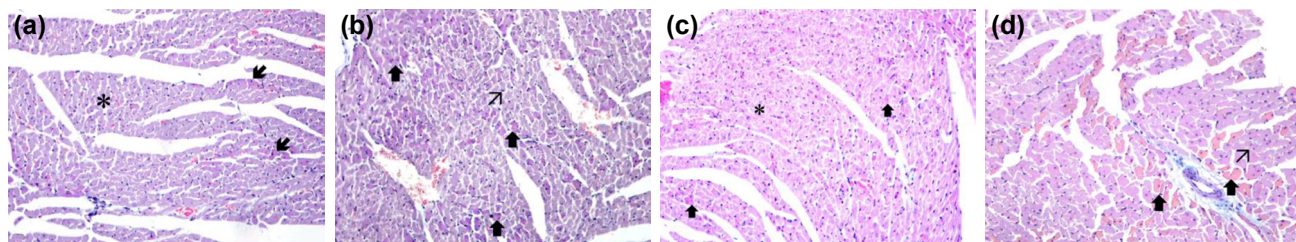
Degeneration, necrosis, and hemorrhage foci of the myocardium were as follows:

**Control group:** In general, there were no anomalies in the heart muscle cells and few degenerative and necrotic cells were identified. Pyknosis of cell nuclei was observed in addition to acidophilic staining of cytoplasmic proteins (Fig. 2a).

**Trauma group:** Foci of degeneration and necrosis were observed in addition to increased hemorrhages in myocytes as compared to the control group (Fig. 2b).

**Resveratrol group:** As compared to the control group, there were no significant differences in the tissue (Fig. 2c).

**Resveratrol + trauma group:** As compared to the control group, degeneration, pyknosis, and necrosis were present. In the histopathological examination, there were no significant differences between this group and the trauma group (Fig. 2d)



**Figure 2.** (a) Control group, (b) trauma group, (c) resveratrol group, (d) resveratrol + trauma (Crossman, trichrome dyeing); asterisk: normal heartbeat, thick arrow: necrotic heartbeat cells, thin arrow: degenerative heartbeat cells, x20.



**Table 1.** Mean immunohistochemical reaction intensities of iNOS ve TNF- $\alpha$

	Control group	Trauma group	Resveratrol group	Resveratrol + trauma group
Inducible nitric oxide synthase	++	+++	+	++
Tumor necrosis factor- $\alpha$	+	++	+	+

No staining (-), poor staining (+), moderate staining (++) and severe staining (+++).

**Table 2.** Serum Tnl, NT pro-BNP, and endocan levels according to groups

	Troponin I (ng/mL)	NT pro-BNP (ng/mL)	Endocan (ng/mL)
Control group	234.3±26.6	595.8±74.7	207.9±61 <sup>a</sup>
Trauma group	206.5±20.7	632.8±111	408.8±39.8 <sup>b</sup>
Resveratrol group	213.9±23	593.7±92.9	472.6±50.2 <sup>b</sup>
Resveratrol + trauma group	222.1±43.4	481±224.9	710.5±214.3 <sup>c</sup>
P	0.361	0.223	<0.001

Values are expressed as means±standard deviation, n=7 for each group. Tnl: Troponin I; NT pro-BNP: N- terminal pro-brain natriuretic peptide.

### Immunohistochemical Results

Analysis of the tissue preparations of each of the groups revealed immunoreactivity of antibodies in heart muscle cells and intracytoplasmic staining.

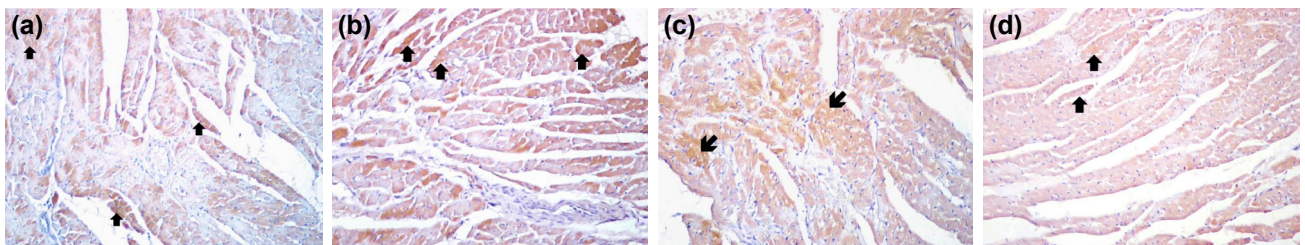
**iNOS:** In the between-group comparison, the intensity of staining/immunoreaction in the control group and resveratrol + trauma group was similar (medium intensity). The intensity of staining/immunoreaction was weak in the resveratrol group as compared to other groups. The most severe reaction was detected in the trauma group (Table 1, Fig. 3).

**TNF- $\alpha$ :** Severity of staining/immunoreaction (moderate) in

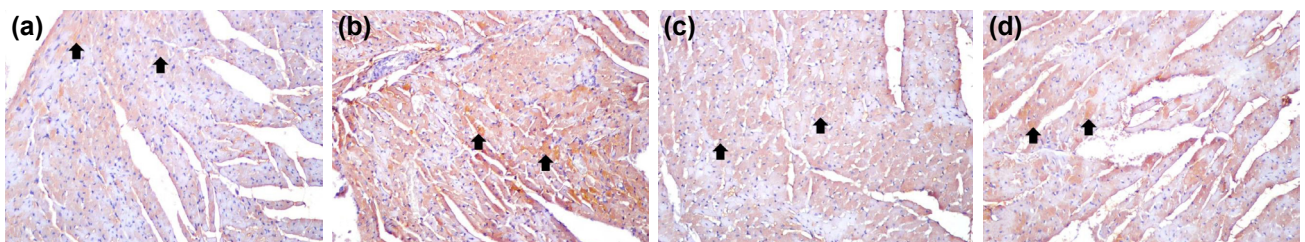
the trauma group was more pronounced than that in the other groups. The reaction intensities in the other three groups were similar to each other (weak) (Table 1, Fig. 4).

### Biochemical Results

The serum values of Tnl, NT pro-BNP, and endocan, in addition to statistical differences in these measurements, are shown in Table 2. The values of Tnl did not differ between the groups (p=0.361). Similarly, there was no between-group difference in NT pro-BNP values (p=0.223). However, the mean values of endocan differed between the groups (p<0.001). The lowest mean value was obtained in the control group. There was no difference in endocan values between the



**Figure 3.** (a) Control group, (b) trauma group, (c) resveratrol group, (d) resveratrol + trauma group (iNOS), arrow: immunopositive cardiomyocytes, x20.



**Figure 4.** (a) Control group, (b) trauma group, (c) Resveratrol group, (d) Resveratrol + trauma group (TNF  $\alpha$ ), arrow: immunopositive cardiomyocytes, x20.

trauma and resveratrol groups. The mean endocan value in the resveratrol + trauma group was higher than that of all the other groups.

## DISCUSSION

The effects of resveratrol on many cardiac diseases have been investigated in clinical and experimental studies.<sup>[1,2]</sup> One study reported the positive effects of resveratrol on ischemia-reperfusion injury and myocardial ischemia.<sup>[21]</sup> Zheng et al.<sup>[21]</sup> reported that resveratrol attenuated hypoxia-reperfusion injury induced in rats and that resveratrol had antiaging properties. Similarly, Hashemzaei et al.<sup>[22]</sup> found that resveratrol reduced cardiotoxicity-induced apoptosis in rats after carbon monoxide exposure and that it had a protective effect. Other studies reported that resveratrol had many positive effects on hypertension, metabolism, and inflammatory processes.<sup>[5,9]</sup> Our literature review did not reveal any studies on the effect of resveratrol on heart failure after blunt chest trauma.

Blunt chest trauma results in various types of damage, such as myocardial contusions, hematomas, ventricular rupture, ventricular septal defects, and valvular damage in the heart. Myocyte damage, hemorrhages, and edema may be observed at the microscopic level.<sup>[11]</sup> Blunt chest trauma also results in the onset of inflammatory processes and release of mediators, leading to life-threatening hemodynamic changes and arrhythmias. Heart injury after blunt chest trauma is associated with an increase in mortality rates.<sup>[10,11]</sup> The present study examined the anti-inflammatory efficacy of resveratrol in cardiac damage induced by blunt chest trauma.

Previous research on the chain of reactions following blunt chest trauma reported a rapid increase in proinflammatory cytokines.<sup>[12]</sup> Research also showed that TNF- $\alpha$  levels increased in the presence of myocardial damage, such as cardiac arrest, sepsis, and multiple organ dysfunction syndromes and that blockade of TNF- $\alpha$  had a therapeutic effect.<sup>[23]</sup> In the present study, the immunoreactivity of TNF- $\alpha$  in the post-traumatic heart was severe, whereas the immunoreactivity of TNF- $\alpha$  in the resveratrol + trauma group was weak. Although various studies have drawn similar conclusions about the association of proinflammatory cytokines with the inflammatory process, there is discord concerning the effect of nitric oxide (NO). For example, Bradamante et al.<sup>[24]</sup> found that resveratrol reduced cardiac ischemia and reperfusion injury by upregulation of NO. Zhang et al.<sup>[4]</sup> reported that resveratrol was effective in endotoxemia-induced lung injury by reducing oxidative and nitric stress. They showed that resveratrol inhibited the formation of peroxynitrite by reducing iNOS expression and oxidative damage. NO played a key role in the maintenance of endothelial cell function. NO showed antioxidant properties by binding to superoxide groups, resulting in the formation of oxidants, such as peroxynitrite, which has a long half-life.<sup>[5]</sup> However, this did not have a significant effect on physiological conditions.

Previous research demonstrated that in pathological conditions, endotoxins, cytokines, and TNF- $\alpha$  induced a 10-fold increase in NO levels by triggering upregulation of iNOS, resulting in the production of NO and peroxynitrite and increased oxidative damage.<sup>[4,25]</sup> In the present study, the increase in TNF- $\alpha$  levels after trauma may have triggered iNOS formation. When the immunoreactivity of iNOS was evaluated, the most intense reaction occurred in the trauma group, whereas immunoreactivity in the resveratrol + trauma group was weak. Resveratrol showed anti-inflammatory and antioxidant properties by reducing TNF- $\alpha$  levels and iNOS production.

The present study investigated the serum level of endocan in relation to the inflammatory process. Previous studies examined the association of endocan with heart disease.<sup>[13,26]</sup> In a study of 164 patients, Wang et al.<sup>[27]</sup> reported that serum levels of endocan were correlated with the presence and severity of coronary artery disease. Balta et al.<sup>[13]</sup> reported that vascular inflammation played an important role in the pathophysiology of hypertension and that the increased level of endocan may be indicative of untreated hypertension. Similar studies reported that endocan can be used as a biomarker in the diagnosis and follow-up of cardiovascular diseases.<sup>[13,26]</sup> They also suggested that endocan induced endothelial activation or dysfunction in endothelium-derived diseases and that it may serve as a biomarker of inflammation in diseases of vascular origin.<sup>[13-15]</sup> Although many studies concluded that an increase in the serum level of endocan was a sign of a worsening disease, there is discord in the literature on this topic.<sup>[13-15]</sup> Mikkelsen et al.<sup>[16]</sup> concluded that decreased endocan levels were associated with progression to acute lung injury in major trauma patients. They attributed this finding to a possible blockade of endocan-mediated leukocyte migration to the lung. In the present study, the increase in serum endocan levels was the same in both the trauma and resveratrol groups. The highest endocan level was observed in the resveratrol + trauma group. Post-traumatic endothelial activation may have triggered the release of endocan. However, the increase in endocan in the resveratrol group and resveratrol + trauma group in the present study cannot be explained based on the current findings. Although many investigators have suggested that endocan may serve as a biomarker in various diseases, in the present study, the serum endocan level was not correlated with the inflammatory process, as it was increased in both the only-trauma and resveratrol treatment groups.

Natriuretic peptides are proteins released in the myocardium in response to overloading or pressure loading. The serum level of Tnl is a biomarker of myocyte damage, with levels increasing after muscle damage.<sup>[28]</sup> Studies on the use of natriuretic peptides, either alone or together with Tnl as biomarkers in the diagnosis of different cardiac diseases, are ongoing.<sup>[28,29]</sup> In a study conducted in 2015, Dogan et al.<sup>[28]</sup> evaluated NT pro-BNP and Tnl levels in heart damage after blunt chest trauma in rats and reported that NT pro-BNP

was significantly increased in the trauma group as compared with that of a control group. They suggested that NT pro-BNP could be used as a diagnostic test for heart failure after blunt chest trauma. In the present study, the histopathological examination revealed myocyte damage and necrotic areas in the trauma group. The severity of iNOS and TNF- $\alpha$  immunoreactivity/staining was significantly higher in the trauma group as compared to that of all the other groups. However, there was no significant difference between the groups in terms of NT pro-BNP and Tnl levels. The time at which the blood samples were obtained may explain this finding. Dogan et al.<sup>[28]</sup> took blood samples in the 5th hour after trauma in their study. In the present study, blood samples were taken 24 hours after the induction of trauma in rats. Further research is needed to investigate the association between the time of blood sampling and the use of serum NT pro-BNP and Tnl as a diagnostic test for cardiac injury in patients with blunt chest trauma.

## Conclusion

The present study showed that resveratrol had anti-inflammatory and antioxidant effects in lung injury after blunt chest trauma and that it contributed to the treatment process. The serum level of endocan was not correlated with the inflammatory process in either the trauma group or resveratrol + trauma group. We believe that there is a need for further studies on the clinical use of endocan as a biomarker of inflammation in cardiac disease.

**Conflict of interest:** None declared.

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## DENEYSSEL ÇALIŞMA - ÖZET

### Sıçanlarda künt göğüs travma sonrası oluşan kalp hasarı üzerine resveratrolün tedavi edici etkisinin ve endokanın enflamasyonda bir biyobelirteç olarak potansiyel rolünün değerlendirilmesi

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**AMAÇ:** Bu çalışma, sıçanlarda künt göğüs travmasına bağlı gelişen kardiyak hasar üzerine resveratrolün terapötik etkisini ve endokanın enflamasyon sürecinde bir biyobelirteç olarak kullanılmasını araştırmıştır.

**GEREÇ VE YÖNTEM:** Sıçanlar randomize olarak aşağıdaki dört gruba ayrıldı (her grupta, n=7): bir kontrol grubu (tedavi veya travma olmadan); travma uygulanan grup (travma grubu); resveratrol grubu (resveratrol, [0.3 mg/kg] intraperitoneal [i.p.] yol grubu yoluyla uygulandı); ve resveratrol + travma grubu (travmanın uygulanmasından 1 saat önce i.p. yolla resveratrol [0.3 mg/kg] verilen).

**BULGULAR:** Travma grubundaki tümör nekroz faktörü- $\alpha$  ve indüklebilir nitrik oksit sentazın immünreaktivitesi artarken, resveratrol + travma grubundaki reaksiyon şiddeti azaldı. Grupların ortalama endokan değerleri farklıydı ( $p<0.001$ ). Resveratrol + travma grubundaki ortalama endokan ortalaması diğer gruplardan daha yüksekti.

**TARTIŞMA:** Resveratrol, künt göğüs travması sonrası akciğer hasarında anti-enflamatuvar ve antioksidan etkilere sahip olup tedavi sürecine katkıda bulunmuştur. Künt göğüs travması sonrası oluşan kardiyak hasarda enflamasyonun takibinde endokanın bir biyobelirteç olarak klinik kullanımı ile ilgili daha fazla çalışma yapılması gerektiğine inanıyoruz.

**Anahtar sözcükler:** Endokan; kalp hasarı; künt göğüs travması; resveratrol.

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