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HSF1 and NF-κB p65 participate in the process of exercise preconditioning attenuating pressure overload-induced pathological cardiac hypertrophy

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ABSTRACT

Pathological cardiac hypertrophy, often accompanied by hypertension, aortic stenosis and valvular defects, is typically associated with myocyte remodeling and cardiac dysfunction. Exercise preconditioning (EP) has been proven to enhance the tolerance of the myocardium to cardiac ischemia-reperfusion injury. However, the effects of EP in pathological cardiac hypertrophy are rarely reported. 10-wk-old male Sprague–Dawley rats (n = 80) were randomly divided into four groups: sham, TAC , EP + sham and EP + TAC. Two EP groups were subjected to 4 weeks of treadmill training, and the EP + TAC and TAC groups were followed by TAC operations. The sham and EP + sham groups underwent the same operation without aortic constriction. Eight weeks after the surgery, we evaluated the effects of EP by echocardiography, morphology, and histology and observed the expressions of the associated proteins. Compared with the respective control groups, hypertrophy-related indicators were significantly increased in the TAC and EP + TAC groups ($p < 0.05$). However, between the TAC and EP + TAC groups, all of these changes were effectively inhibited by EP treatment ($p < 0.05$). Furthermore, EP treatment upregulated the expression of HSF1 and HSP70, increased the HSF1 levels in the nuclear fraction, inhibited the expression of the NF-κB p65 subunit, decreased the NF-κB p65 subunit levels in the nuclear fraction, and reduced the IL2 levels in the myocardia of rats. EP could effectively reduce the cardiac hypertrophic responses induced by TAC and may play a protective role by upregulating the expressions of HSF1 and HSP70, activating HSF1 and then inhibiting the expression of NF-κB p65 and nuclear translocation.

1. Introduction

At present, cardiovascular disease remains the major cause of death worldwide. Pathological cardiac hypertrophy, accompanied by hypertension, aortic stenosis and valvular defects, is typically associated with myocyte remodeling, fibrotic replacement, and cardiac dysfunction, together increasing the risk of heart failure and sudden death. The beneficial effects of regular physical activity on cardiovascular health have been well defined. Exercise preconditioning (EP), a physiologic favorable adaptation in many organs, including the heart, has been proven to increase the myocardial mechanical load and to enhance the tolerance of myocardium to cardiac ischemia-reperfusion injury (IRI) [1,2]. EP is one of only a few interventions known to improve cardiac function rather than merely delaying disease progression [3,4]. The transverse aortic constriction (TAC) model is performed by banding the aorta between the innominate artery and the left carotid artery and is a convincing method for producing pressure overload-induced

Abbreviations: EP, exercise preconditioning; TAC, transverse aortic constriction; LVWD, LV wall thickness in end diastole; LVIDd, LV internal dimension at end-diastole; CSA, cross-sectional area; HW/BW, heart weight-to-body weight ratio; HW/TL, heart weight-to-tibia length ratio; BNP, brain natriuretic peptide; HSF1, heat shock transcription factor 1; Hsp70, heat shock protein 70; NF-κB p65, nuclear transcription factor-κB p65.

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pathological hypertrophy and heart failure [5]. Similar to aortic stenosis and hypertension, TAC initially leads to compensated hypertrophy of the heart, which often is associated with a temporary enhancement of cardiac contractility. Over time, however, the response to the chronic hemodynamic overload becomes maladaptive, resulting in cardiac dilatation and heart failure. At present *EP has been less reported in pathological cardiac hypertrophy*, and the related molecular mechanisms underlying the cardioprotective effects of EP have not been well defined.

It has been reported that the overexpression of heat shock transcription factor 1(HSF1) in the heart preserves cardiac function [6], whereas reduced HSF1 expression impairs early adaptive responses to acute pressure overload. Nuclear transcription factor(NF)-κB is a ubiquitous transcription factor that regulates the relative genes involved in cardiac remodeling, antiapoptotic [7] and inflammatory responses [8] and can play an important role in the pathophysiology of myocardial IRI, atherosclerosis and heart failure. The activation of the NF-κB pathway plays a key role in the development of cardiac hypertrophy, and the inhibition of the NF-κB pathway may promote the regression of cardiac hypertrophy induced by pressure overload [9–12]. Therefore, *we present the hypothesis that EP can alleviate pressure overload-induced pathological cardiac hypertrophy in rats and that HSF1 and NF-κB signaling pathways participate in the process of EP,* alleviating pressure overload-induced pathological cardiac hypertrophic responses.

In the present study, we established rat models of cardiac hypertrophy induced by TAC after EP and examined the expressions of brain natriuretic peptide (BNP), HSF1, heat shock protein (Hsp)70, and transcription factor κB (NF-κB) p65 in the hearts to verify this hypothesis.

2. Materials and methods

2.1. Animal models

Eighty male Sprague–Dawley rats (ages 10 wks; s&p - Shall Kay Laboratory Animal Co., LTD, Shanghai, China) were used for this study. The experimental protocols were approved by the Animal Care and Use Committee of Second Military Medical University and were in compliance with the Guidelines for the Declaration of Helsinki. In brief, all animals were randomly divided into four groups (20 rats per group): the sham group, TAC group , EP-treated sham group (EP + sham group) and EP-treated TAC group (EP + TAC group). According to the Bedford standard [13], rats for EP training were subjected to moderate-intensity exercise (approximately 60% of their maximal aerobic velocity) [14] on a motor-driven treadmill (Hangzhou, China) for 4 wks. In the first 5 days, these rats were trained for 0% grade, 40 min/day at 15 m/min, and the duration and intensity increased daily until the animals were trained for 60 min at 18 m/min, 0% grade. Thereafter, exercise intensity was kept constant at a moderate level during each training period (5 days per week). All post-training experiments in trained rats were performed for 48 h after the last exercise training to avoid the acute effects of exercise. The other two groups of rats remained at sedentary during the training period. After EP, the rats from the EP + TAC and TAC groups were anesthetized with barbital sodium administered intraperitoneally at 200 mg/kg body weight and completed by tying a 3-0 silk suture over an 8 gauge needle to produce pressure overload-induced pathological cardiac hypertrophy, as previously described [15–18]. The sham and EP + sham groups underwent the same operations without aortic constriction. All rats were placed on a heating pad at 37 °C until they had completely recovered from the anesthesia, and penicillin was used to prevent infection. Buprenorphine (0.1–2.5 mg/kg; SQ) was administered immediately after surgery and during post-operative recovery. Eight weeks after the surgery, sham, TAC, EP + sham and EP + TAC rats were examined with echocardiography, weighed and decapitated under anesthesia, followed by the collection of their cardiac tissues and tibia length measurements. Heart weight-to-body weight (HW/BW) ratios and the heart weight-to-tibia length ratio (HW/TL) were recorded at the time of tissue collection.

2.2. Echocardiography and hemodynamic measurements

Rats (n = 10, per group) were anesthetized by barbital sodium, and transthoracic echocardiographic measurements were carried out by an animal-specific instrument (VisualSonics Vevo770, VisualSonics Inc., Toronto, Canada). All measurements, averaged over five consecutive cardiac cycles, were performed by two experienced technicians unaware of experimental group identities. Mean arterial pressure (MAP) was evaluated as described [19]. A microcatheter pressure transducer was inserted into the right common carotid artery, and the transducer was connected to a Power Laboratory system to record the MAP (n = 5, per group).

2.3. Morphology and histological analyses

Hearts (n = 10, per group) were weighed, perfused with PBS and fixed with 4% polyformaldehyde for global morphometry and then with 10% formalin for further histological analysis. Paraffin-embedded hearts were sectioned at 4–6 μm thickness and stained with hematoxylin and eosin (H-E). Cardiomyocyte morphology and histology were visualized under high magnification to assess the cross-sectional area (CSA) using a video camera (Leica Qwin 3) attached to a micrometer. Images were analyzed using an Image J (NIH, USA). The CSA of cardiomyocytes was measured from 5 hearts in each group, and 5 randomly chosen fields were evaluated from each cross section of the LV free wall.

2.4. Quantitative real-time polymerase chain reaction

Total RNA was isolated from the LV of the animal models (n = 6, per group) using TRIzol reagent (Invitrogen, California, USA). SYBR Green qRT-PCR (Takara Bio Inc., Otsu, Japan) was used with reverse and forward primers designed specifically for each of the mRNAs (Table 1). qRT-PCR primers were compounded and purchased from Sangon Biological (Shanghai, China), and the gene expression was normalized to that of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) for mRNA. The expression of the target genes was quantified by qRT-PCR using One Step SYBR PrimeScript RT-PCR Kit II (Takara) on an ABI StepOne Real-Time PCR System (Life Technologies) with conventional protocols. All data were analyzed using the threshold cycle relative quantification (ΔΔCT) method.

2.5. Western blot analysis

Total proteins from the LV of rats (n = 6, per group) were separated using RIPA lysis buffer containing 1 mmol/l protease and

Table 1
Primers for the quantitative real-time polymerase chain reaction.

Gene	Forward	Reverse
GAPDH	5′- GCCATCACTGCCACTCAGAA-3′	5′- GGCATGTCAGATCCACAACG-3′
BNP	5′-CCGGATCCAGGAGAGACTTC-3′	5′-TCTGCAGCCAGGAGGTCTTC-3′
HSP70	5′- GTTCGACGTGTCCATCCTGA -3′	5′- ACTCCTCCACGAAGTGGCTC -3′

phosphatase inhibitor (Pierce, USA). The isolation of nuclear proteins was performed using the Nuclear Extraction Kit from Merck. Whole-cell lysates or nuclear extracts were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis and transferred to nitrocellulose membranes (Millipore, USA) using the previously described methods [20].

2.6. Statistics

Data are expressed as the means ± standard deviation (means ± SD). All computations were carried out using the SPSS version 18.0 software for Windows (SPSS Inc. IL, USA). The statistical significance of differences among experimental groups was evaluated by one-way analysis of variance (ANOVA). When the ANOVA revealed significant between-group differences, a post hoc analysis was performed using Bonferroni's method of multiple comparisons. Single between-group comparisons were made using Student's t-tests. A two-tailed P value of 0.05 was considered statistically significant.

3. Results

3.1. EP mitigates pressure overload-induced pathological remodeling

Eight weeks after TAC, the MAP was increased in the TAC and EP + TAC groups (Fig. 1A). Compared with those of the respective control group, our experimental data reflect severe cardiac hypertrophy($p < 0.05$), as characterized by an increase in LV wall thickness in end diastole (LVWD) (Fig. 1B), heart size, HW/BW, HW/TL(Fig. 1C), and cross-sectional area of the cardiomyocytes(CSA) (Fig. 1D), particularly in conjunction with a lowered LV internal dimension at end-diastole (LVIDd) and LV fractional shortening (Fig. 1B) in the TAC and EP + TAC group at 8 weeks after operation. QRT-PCR and western blot analysis for fetal gene-BNP [21] expressions in the LV (Fig. 1E) revealed a significant pathological cardiac hypertrophic response to the pressure overload. However, in the TAC and EP + TAC groups, these changes to the parameters assessing cardiac hypertrophy were significantly attenuated by EP treatment (Fig. 1A–E).

3.2. Effects of EP on the expressions of HSF1 and HSP70 in the hypertrophic hearts

The expression of HSF1 was determined using QRT-PCR and western blotting to reflect the effects of EP on TAC stimulation. TAC significantly reduced the expression of HSF1 compared with sham ($p < 0.01$) (Fig. 2A); however, EP treatment significantly increased the expression of HSF1 ($p < 0.05$). Additionally, to evaluate the activation of HSF1, HSF1 levels in the nucleus were explored by western blotting. Compared with sham, nuclear HSF1 levels were decreased in the TAC group but significantly increased in the EP + TAC group (Fig. 2B). HSF1 usually induces the expression of HSPs, including HSP70. Because HSP70 has received much attention as a clinical marker in heart failure, increased circulating levels of HSP have been reported to be associated with disease severity. To investigate whether the expression of HSP70 changes during the periods of animal cardiac hypertrophy, we examined the expression levels of HSP70 along with the QRT-PCR and western blotting analyses. The results showed that, compared with the sham group, TAC induced the mRNA and protein (Fig. 2C) levels of HSP70; still, these decreases were significantly improved by EP treatment ($P < 0.01$).

3.3. Effects of EP on the NF-κB pathway in the heart during pathological cardiac hypertrophy

NF-κB is generally well known to worsen cardiac remodeling or dysfunction by activating pro-inflammatory pathways. Previous studies have shown that the activation of NF-κB is essential for the development of cardiac hypertrophy induced by pressure overload in vivo. Our data show that, compared with the sham group, cytoplasm NF-κB p65 protein levels were significantly increased in the TAC group but were markedly decreased in the EP + TAC group, compared to the TAC group (Fig. 3A). To further investigate the effects of EP on the nuclear translocation of NF-κB in hypertrophic cardiac tissue, an important step in the activation of NF-κB pathway, the NF-κB p65 subunit levels in the nucleus were explored by western blotting analysis. Compared with the sham group, nuclear NF-κB p65 subunit levels were increased in the TAC group, but these changes were significantly inhibited by EP treatment (Fig. 3B). IL2 protein levels were significantly more decreased in the EP + TAC group than in the TAC group (Fig. 3C).

4. Discussion

Because pathological cardiac hypertrophy is an independent risk factor for cardiovascular morbidity and mortality [22], the attenuation of pathological cardiac hypertrophy is of high clinical significance. Regular physical exercise, which is known to improve function in heart failure patients [4,23], activates a complex network of molecular events that can protect the heart in settings of stress. In this study, we determined that EP could effectively reduce the cardiac hypertrophic responses induced by TAC and may play a protective role by upregulating the expressions of HSF1 and HSP70, activating HSF1 and finally inhibiting the expression of NF-κB p65 and nuclear translocation.

EP, as a physiologically favorable adaptation, increases the myocardial mechanical load and is accompanied by a positive alteration in the stroke volume and sympathetic nervous system activity. Here, we showed that LV wall thickness and HW/BW were significantly increased during cardiac hypertrophy induced by TAC-triggered pressure overload at 8 wks after TAC. In the process of cardiac hypertrophy, BNP, a fetal gene, is reactivated. Recent evidence suggests that BNP as a marker of cardiac failure has been increasingly used for the diagnosis of cardiac failure, differential diagnosis, risk stratification, prognosis and treatment guideline. Our data also show that the relative expression levels of BNP mRNA and proteins in the hypertrophic cardiac tissue were inhibited by EP treatment. These data suggest that EP could rescue TAC-induced cardiac hypertrophy, improving cardiac function.

It has been reported that HSF1 not only plays an important role in excise-induced physiological cardiac hypertrophy [6] but is also involved in many pathological responses [24,25]. Studies have demonstrated that HSF1 regulates Hsps gene expression [26] and that Hsp70 is upregulated in the heart in response to exercise [27] and has been linked with cardiac protection. Indeed, we found that the cytoplasm HSF1 and HSP70 expressions in the EP + sham and EP + TAC groups were markedly higher than in the TAC group. The overexpression of activated HSF1 in the heart can prevent cardiomyocyte death and cardiac fibrosis in response to sustained pressure overload, thereby preserving cardiac function [6]. In the present study, we found that the activation of HSF1 in the EP + sham and EP + TAC groups was significantly higher than in the TAC group on the basis of nuclear HSF1 expression levels, suggesting that exercise promotes the sustained activation of HSF1, leading toward a constitutive expression of Hsp70 in heart.

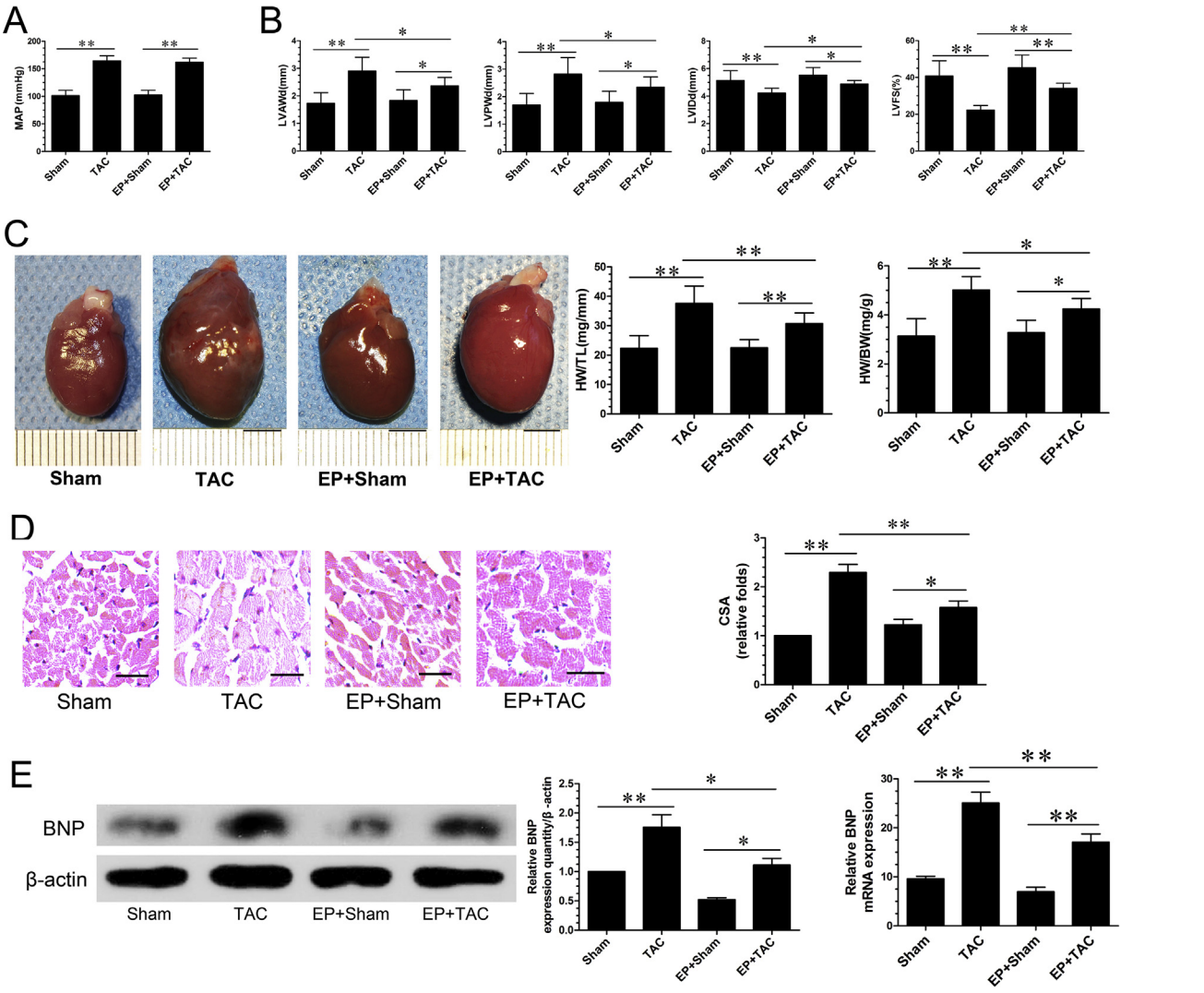

Fig. 1. EP attenuated the pathological cardiac hypertrophy induced by pressure overload. A: MAP recordings; Recordings were shown from 5 rats in each group; B: Echocardiographic analysis with representative M-mode tracings from 10 rats in each group. All echocardiograghic data are shown as means ± SD; LVAWd, LV anterior wall thickness at end-diastole; LVPWd, LV posterior wall thickness at end-diastole; LVIDd, LV internal dimension at end-diastole; LVFS, LV fraction shortening; C: Heart morphology and weight; representative global heart photographs (scale bar: 5 mm); heart weight-to-body weight radio (HW/BW) and heart weight-to-tibia length ratio(HW/TL) measured from 10 rats in each group; D: H-E stained LV sections of rats; scale bar: 100 μm; cross sectional area (CSA) of cardiomyocyte measured from 5 hearts in each group; E: The expressions of BNP were confirmed by qPCR and Western blot. The mRNA expression of BNP was quantified as the ratio of BNP to GAPDH and expressed as 100% of sham. Representative photographs are shown of the protein expression of BNP, and β-actin in whole cell lysate was used as the loading control. Data are shown as means ± SD from 6 individual experiments. $^{*}p < 0.05$, $^{**}p < 0.01$.

The NF-κB pathway has been shown to mediate cardiac hypertrophy and maladaptive remodeling. It has been reported that persistent myocyte NF-κB p65 subunit activation in cardiac failure exacerbates cardiac remodeling by imparting pro-inflammatory, profibrotic, and pro-apoptotic effects [11,28]. In addition, the NF-κB p65 subunit is a mainly classical signaling pathway and plays an important role in the development of inflammation [29]. It has been shown that HSF-1 can down-regulate the expression of NF-κB p65, suppress the nuclear levels of NF-κB p65, prevent NF-κB p65 translocation [30] and mediate the competitive inhibition of NF-κB nuclear binding [31]. HSPs can also interfere with the release of NF-κB p65 [32,33]. To better understand the effects of EP on cardiac hypertrophy, we investigated the NF-κB pathway in this research. We demonstrated that the EP-treated group showed a lower nuclear NF-κB p65 subunit protein level than the non-EP group, whereas the TAC group showed a higher nuclear NF-κB p65 subunit protein level than the sham group. Thus, it could be inferred that HSF1 regulated these signaling molecules, controlling the release of NF-κB p65. Taken together, these findings provide strong evidence that EP treatment attenuates pressure overload-induced pathological cardiac remodeling and cardiac dysfunction through the upregulation of the expression of HSF1 and HSP70, the activation of HSF1 and the inhibition of the NF-κB signaling pathway. This knowledge is beneficial to patients with cardiovascular disease who are either unable or unwilling to undertake regular physical activity intervention programs; its content is furthermore essential for the development of novel and viable therapeutic intervention strategies.

In summary, the present study suggests that EP can effectively reduce the cardiac hypertrophic responses induced by TAC and may play a protective role in the upregulation of the expressions of HSF1 and HSP70, in the activation of HSF1 and in the inhibition of NF-κB p65 expression and nuclear translocation.

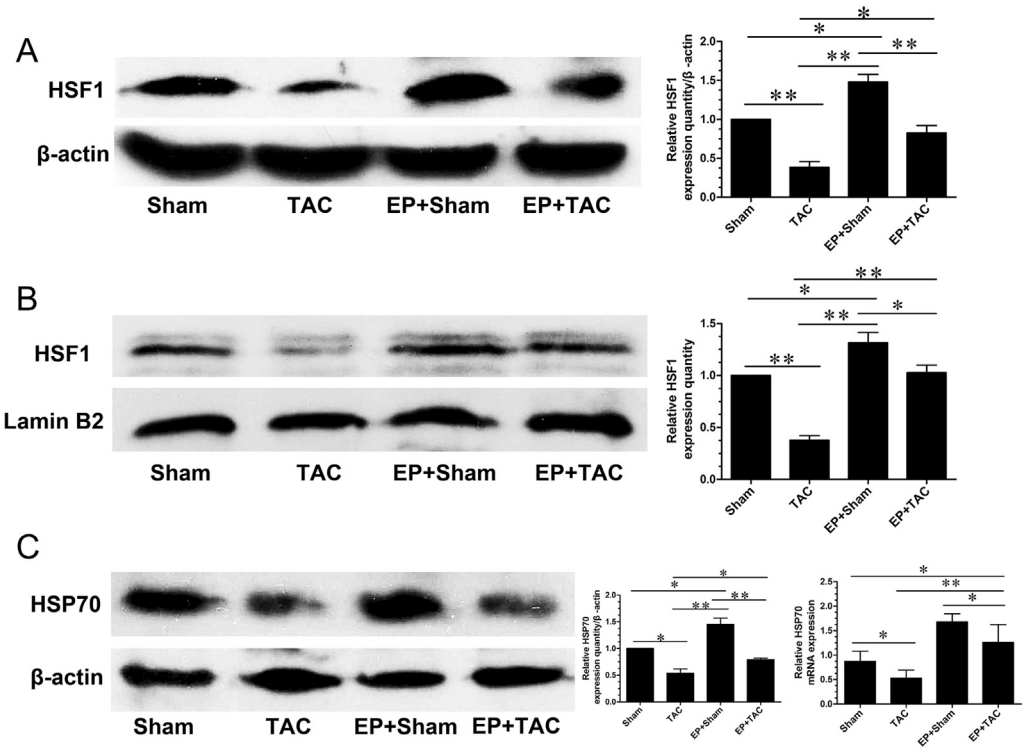

Fig. 2. Effects of EP on the expression of HSF1 and HSP70 in the hypertrophic hearts subject to TAC. A. Cell lysate HSF1 expression was detected by Western blot; representative photographs are shown of the protein expression of HSF1; and expression of HSF1 was quantified as the ratio of HSF1 to β-actin and expressed as 100% of sham. B. Detection of nuclear HSF1 expression by Western blot and nuclear HSF1 levels, with the expression of HSF1 quantified as the ratio of HSF1 to lamin B2 and expressed as 100% of sham. C. Detection of cell lysate HSP70 expression by Western blot; representative photographs of the protein expression of HSP70; and the expression of HSP70 was quantified as the ratio of HSP70 to β-actin and expressed as 100% of sham. The mRNA expression of HSP70 was quantified as the ratio of HSP70 to GAPDH and expressed as 100% of sham. Data are shown as the means ± SD from 6 individual experiments. $^{*}p < 0.05$, $^{**}p < 0.01$.

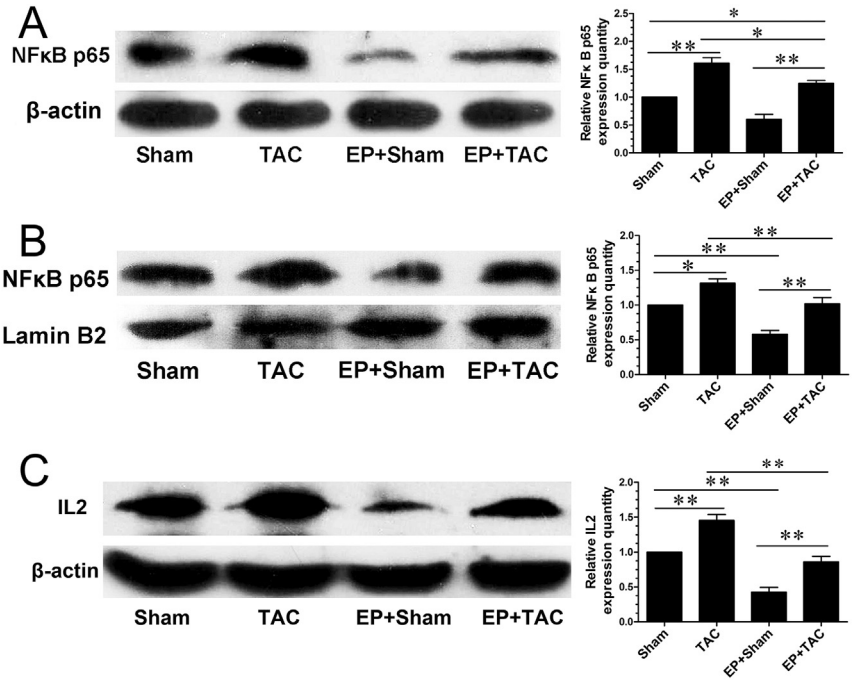

Fig. 3. The effect of EP on the myocardial NF-κB signaling pathway in rats subjected to TAC. A. Detection of cytoplasm NF-κB p65 subunit expression by Western blot; cytoplasm NF-κB p65 subunit levels; and the expression of NF-κB p65 subunit, quantified as the ratio of NF-κB p65 to β-actin and expressed as 100% of sham. B. Nuclear NF-κB p65 subunit expression was detected by Western blot, and nuclear NF-κB p65 subunit levels were quantified as the ratio of NF-κB p65 to lamin B2 and expressed as 100% of sham. C. Cell lysate IL2 expression was detected by Western blot; representative photographs were taken of the protein expression of IL2; and the expression of IL2 was quantified as the ratio of IL2 to β-actin and expressed as 100% of sham. Data are shown as means ± SD from 6 individual experiments. $^{*}p < 0.05$, $^{**}p < 0.01$.

Study limitations

This study has two limitations. First, a missing element is preoperative echocardiography on these experimental animals. Second, there is yet no scientific consensus in the critical point of intensity and duration of EP protective effect.

Conflicts of interest

The authors have declared that no competing interests exist.

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Transparency document

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