Anti-apoptotic and pro-survival effects of exercise training on hypertensive hearts

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Huang C-Y, Yang A-I, Lin Y-M, Wu F-N, Lin JA, Chan Y-S, Tsai F-J, Tsai C-H, Kuo C-H, Lee S-D. Anti-apoptotic and pro-survival effects of exercise training on hypertensive hearts. J Appl Physiol 112: 883–891, 2012. First published December 29, 2011; doi:10.1152/japplphysiol.00605.2011.—Background: activated cardiac apoptosis was found in hearts from hypertensive animals, but little information regarding the effects of exercise training on cardiac apoptosis in hypertension is available. The purpose of this study was to evaluate the anti-apoptotic and pro-survival effects of exercise training on hypertensive hearts. Methods: 28 spontaneously hypertensive rats were divided into sedentary group (SHR) or underwent running exercise on treadmill for 1 h/day, 5 sessions/wk, for 12 wk (SHR-EX). Fourteen age-matched Wistar Kyoto rats served as a sedentary normotensive group (WKY). After exercise training or sedentary status, the excited hearts were measured by hematoxylin and eosin staining, terminal deoxynucleotidyl transferase dUTP-mediated nick-end labeling (TUNEL) assay, and Western blotting. Results: fewer TUNEL-positive apoptotic cells were in SHR-EX groups than those in SHR. Protein levels of Fas ligand, Fas death receptor, tumor necrosis factor (TNF-α) receptor 1, Fas-associated death domain (FADD), activated caspase-8, and activated caspase-3 (Fas-dependent apoptotic pathways), as well as Bid, t-Bid, Bad, p-Bad, Bak, cytochrome c, activated caspase 9, and activated caspase-3 (mitochondria-dependent apoptotic pathways) were decreased in the SHR-EX group compared with the SHR group. Protein levels of IGF-1, IGF-1R, p-PI3K, p-Akt, p-Bad, and Bcl2 (cardiac pro-survival pathway) become more activated in SHR-EX groups than SHR and WKY. Conclusions: exercise training prevented hypertension-enhanced cardiac Fas-dependent and mitochondria-dependent apoptotic pathways and enhanced cardiac pro-survival pathway in rat models. Our findings demonstrate new therapeutic effects of exercise training on hypertensive hearts for preventing apoptosis and enhancing survival.

HYPERTENSION IS THE MOST COMMON risk factor for congestive heart failure (12, 26). Hypertension is associated with impaired left ventricle diastolic function, which is independent of the effect of obesity and other covariates (20). Previous evidence demonstrates that cardiomyocyte apoptosis is abnormally stimulated in the hearts of animals and humans with arterial hypertension (6). More activated cardiomyocyte apoptosis and cardiac apoptosis in hypertensive models were reported from our previous study (10).

Apoptosis, a physiological program of cellular death, may contribute to many cardiac disorders (9, 10). The “extrinsic” Fas ligand or tumor necrosis factor-alpha (TNF-α) dependent (type I) apoptotic pathway is believed to be one of the major pathways directly triggering cardiac apoptosis (3, 9). This pathway is initiated by binding the Fas ligand to the Fas death receptor or by binding TNF-α to TNF receptor 1, which results in the clustering of receptors and initiating an extrinsic pathway (3). Fas ligand and Fas or TNF-α and TNF receptor 1 complex are known to lead to the formation of a death-inducing signal complex starting with recruitment of the Fas-associated death domain (FADD) of the adaptor protein (3). FADD recruits and aggregates the pro-form of caspase-8 and leads to its activation of caspase-8 (2). The activated caspase-8 cleaves pro-caspase-3, which then undergoes autocatalysis to the active form of caspase-3, a principle effector in apoptosis (14, 17). The “intrinsic” mitochondrial-dependent (type II) apoptotic pathway is mediated by internal factors, especially in mitochondrion (3). The mitochondria is the main site of action for members of the apoptosis-regulating protein family exemplified by Bcl-2 family, such as Bax, Bad, t-Bid, and Bak(3). Pro-apoptotic and anti-apoptotic Bcl-2 family members can homodimerize or heterodimerize to each other and appear to interact with and neutralize each other, so that the relative balance of these effectors strongly influences cytochrome c release. When cytochrome c is released from mitochondria into cytosol, it is responsible for activating caspase-9, which further activates caspase-3 and executes the apoptotic program (4). In addition, Bid is one of the key components involved in the intracellular molecule signaling from Fas to mitochondrial apoptotic pathways (1, 3).

Insulin-like growth hormone (IGF1) signaling is reported to contribute to the modulation of survival responses in cardiac tissues. Phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt) are key signaling factors in insulin and IGF1 receptor (IGF1R) (18, 28). Akt is one of the major upstream signal proteins of the Bcl-2 family, and phosphorylated Akt (p-Akt) appears to promote the pro-survival pathway (13).
Bel-2 and phosphorylated-BAD (p-Bad) prevent apoptotic activities (3).

Regular physical activity and exercise training have been regarded as therapeutic approaches in the treatment or prevention of hypertension (15, 25). Exercise training improves cardiac function, functional capacity, and quality of life in patients with cardiovascular diseases (22, 23). Exercise training decreases resting heart rates and, consequently, attenuates high blood pressure in hypertensive rats (27). However, the effect of exercise training on cardiac anti-apoptosis and pro-survival pathways in hypertension is not understood. In the current study, we hypothesized that exercise training may have anti-apoptotic and pro-survival effects on hypertensive hearts.

MATERIALS AND METHODS

Animal model. The study was conducted with 14 Wistar Kyoto rats (WKY) and 28 spontaneously hypertensive rats. The spontaneously hypertensive rats were divided into a sedentary group (SHR) and a group that underwent exercise training on a treadmill for 1 h/day, 5 sessions/wk, for 12 wk (SHR-EX). Ambient temperature was maintained at 22–24°C, and the animals were kept on an artificial 12:12-h light-dark cycle. The light period began at 7:00 A.M. Rats were provided with standard laboratory chow (Lab Diet 5001; PMI Nutrition International, Brentwood, MO) and water ad libitum. All protocols were approved by the Institutional Animal Care and Use Committee of China Medical University, Taichung, Taiwan, and the principles of laboratory animal care (NIH publication) were followed.

Exercise training. The 12-wk exercise training protocol was implemented according to the study of Chen et al. (5). Before the beginning of exercise training, rats from the SHR-EX group had run on a horizontal treadmill (model T510E, Diagnostic and Research Instruments) at the speed of 12 m/min for familiarization. After 1 wk of familiarization, all rats ran on the treadmill for 60 min/session, 5 sessions/wk, for 12 wk. During the training period, the running speed was gradually increased 3 m/min and was maintained at 27 m/min. In contrast, rats from sedentary groups (WKY and SHR) were placed on the treadmill without running for 15 min for each session. To avoid acute effect of exercise training, all animals were killed 48 h after exercise training. Body weight, blood pressure level, and echocardiography were measured before death.

Table 1. Cardiac characteristics of WKY, SHRm group and SHR-EX

<table>
<thead>
<tr>
<th></th>
<th>WKY</th>
<th>SHR</th>
<th>SHR-EX</th>
</tr>
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<tbody>
<tr>
<td>Number of animals</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>BW, g</td>
<td>274 ± 27</td>
<td>310 ± 16†</td>
<td>293 ± 23‡</td>
</tr>
<tr>
<td>WHW, g</td>
<td>0.94 ± 0.13</td>
<td>1.05 ± 0.07†</td>
<td>1.09 ± 0.08‡</td>
</tr>
<tr>
<td>LVW, g</td>
<td>0.72 ± 0.07</td>
<td>0.86 ± 0.06†</td>
<td>0.88 ± 0.08‡</td>
</tr>
<tr>
<td>WHW/BW(×10⁴)</td>
<td>34.68 ± 6.45</td>
<td>33.91 ± 2.66</td>
<td>38.36 ± 2.92‡§</td>
</tr>
<tr>
<td>LVW/BW(×10⁴)</td>
<td>26.51 ± 4.34</td>
<td>27.69 ± 2.09</td>
<td>31.02 ± 2.09§</td>
</tr>
<tr>
<td>LVW/WHW</td>
<td>0.768 ± 0.042</td>
<td>0.820 ± 0.014†</td>
<td>0.812 ± 0.033‡</td>
</tr>
<tr>
<td>WHW/tibia, g/mm</td>
<td>0.025 ± 0.004</td>
<td>0.028 ± 0.002†</td>
<td>0.029 ± 0.003‡</td>
</tr>
<tr>
<td>LVW/tibia, g/mm</td>
<td>0.019 ± 0.002</td>
<td>0.023 ± 0.002‡</td>
<td>0.024 ± 0.003‡</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>136 ± 5</td>
<td>197 ± 7§</td>
<td>181 ± 6‖</td>
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<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>100 ± 5</td>
<td>125 ± 8§</td>
<td>123 ± 5‖</td>
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<tr>
<td>Mean blood pressure, mmHg</td>
<td>112 ± 3</td>
<td>148 ± 4†</td>
<td>142 ± 3‡</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>369 ± 45</td>
<td>441 ± 36†</td>
<td>409 ± 46‡</td>
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<tr>
<td>IVSd, mm</td>
<td>2.02 ± 0.26</td>
<td>2.12 ± 0.24</td>
<td>2.12 ± 0.32</td>
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<td>LVMPd, mm</td>
<td>1.91 ± 0.30</td>
<td>1.73 ± 0.17</td>
<td>1.66 ± 0.20</td>
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<tr>
<td>LVIDd, mm</td>
<td>7.95 ± 1.80</td>
<td>7.43 ± 0.62</td>
<td>7.64 ± 1.05</td>
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<tr>
<td>LVIDs, mm</td>
<td>5.21 ± 1.56</td>
<td>4.77 ± 0.62</td>
<td>4.87 ± 0.80</td>
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<tr>
<td>FS, %</td>
<td>35.01 ± 5.61</td>
<td>35.70 ± 7.24</td>
<td>35.07 ± 4.38</td>
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<tr>
<td>Citrate synthase activity, μmol·min⁻¹·g wet wt⁻¹</td>
<td>1.84 ± 0.03</td>
<td>1.86 ± 0.06</td>
<td>2.26 ± 0.08‡‡</td>
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Values are means ± SE in Wistar Kyoto rat (WKY) and spontaneously hypertensive rat with or without exercise training (SHR and SHR-EX) (n = 8 in each group). BW, body weight; WHV, whole heart weight; LVW, left ventricular weight; FS, fractional shortening; IVSd, interventricular septum at diastole; LVMPd, left ventricular posterior wall thickness at diastole; LVIDd, internal dimension at diastole of left ventricle; LVIDs, internal dimension at systole of left ventricle; FS.: (LVIDd−LVIDs)/LVIDd × 100). *P < 0.05, †P < 0.01 significant differences between WKY and SHR or between WKY and SHR-EX group. ‡P < 0.05 §P < 0.01 significant differences between SHR group and SHR-EX group.
(H&E). After gently rinsing with water, each slide was dehydrated through graded alcohols. Finally, they were soaked in xylene twice. Photomicrographs were obtained using Zeiss Axiophot microscopes. For terminal deoxynucleotidyl transferase dUTP-mediated nick-end labeling (TUNEL) assay, the sections were incubated with proteinase K, washed in PBS, incubated with permeabilization solution, blocking buffer, and then washed twice with PBS. The terminal deoxynucleotidyl transferase and fluorescein isothiocyanate-dUTP for 60 min at 37°C from an apoptosis detection kit (Roche Applied Science, Indianapolis, IN) were used for detection. Then the 4,6-diamidino-2-phenylindole (DAPI) was added for 5 min, and the nucleus position was fluoresced by blue light at 340–380 nm. TUNEL-positive nuclei (fragmented DNA) were fluoresced by bright green light at 450–500 nm. The mean number of TUNEL-positive cells were counted for at least five or six separate fields. 

**Tissue extraction.** Cardiac tissue extracts of eight rats in each group were obtained by homogenizing the left ventricle samples in a lysis buffer at a ratio of 100 mg tissue/1 ml buffer. The homogenates were placed on ice and then centrifuged at 12,000 g for 40 min. The supernatant was collected and stored at −80°C for further experiments.

**Electrophoresis and Western blot.** Protein concentration of cardiac tissue extracts was determined by the Lowry protein assay. Protein samples (40 μg/lane) were separated on a 10% SDS polyacrylamide gel electrophoresis (SDS-PAGE) with a constant voltage of 75 V.
Electrophoresed proteins were transferred to polyvinylidene difluoride (PVDF) membrane (Millipore, Bedford, MA, 0.45 μm pore size) with a transfer apparatus (Bio-red). PVDF membranes were incubated in 5% milk in TBS buffer. Primary antibodies including Fas ligand, Fas, TNF-α, TNF receptor 1, FADD, Bid, t-Bid, Bax, Bad, Bak, cytochrome c, caspase-8, caspase 9, caspase-3, IGF1, IGF1-R, PTEN, p-P13K, Akt, p-Bad, Bcl2, and α-tubulin (Santa Cruz Biotechnology, Santa Cruz, CA) and p-Akt (Cell Signaling Technology, Beverly, MA) were diluted to 1:500 in antibody binding buffer overnight at 4°C. The immunoblots were washed three times in TBS buffer for 10 min and then immersed in the second antibody solution containing goat anti-mouse IgG-HRP, goat anti-rabbit IgG-HRP, or donkey anti-goat IgG-HRP (Santa Cruz Biotechnology) for 1 h and diluted 500-fold in TBS buffer. The immunoblots were then washed three times in TBS buffer for 10 min. The immunoblotted proteins were visualized using an enhanced chemiluminescence ECL Western blotting luminal reagent (Santa Cruz Biotechnology) and quantified using a Fujifilm LAS-3000 chemiluminescence detection system (Tokyo, Japan).

Statistical analysis. All data of heart weight index, blood pressure, echocardiographic index, soleus citrate synthase activity, protein levels, and the percentage of TUNEL positive cells were compared among the WKY, SHR, and SHR-EX groups using one-way ANOVA with preplanned contrast comparison with the control group. WKY and nonexercise SHR served as the negative control and the positive control, respectively. In all cases, $P < 0.05$ was considered significant.

RESULTS

Body weight and cardiac characteristics. The body weight (BW) of SHR is higher than that of WKY, and the body weight in SHR-EX was lower than that in SHR (Table 1). The whole heart weight (WHW), left ventricular weight (LVW), LVW/BW, WHW/WHW, WHW/tibia, and LVW/tibia in SHR and SHR-EX were higher than those in WKY. The WHW/BW and LVW/BW in SHR-EX was higher than those in SHR (Table 1). The systolic blood pressure, diastolic blood pressure, mean blood pressure, and heart rates were increased in SHR compared with WKY. The systolic and mean blood pressures were decreased in SHR-EX compared with SHR (Table 1). Echocardiography showed no difference among three groups, WKY, SHR, and SHR-EX (Table 1). These results of higher citrate synthase activity in SHR-EX indicated that the exercise program in SHR-EX group was effective.

Fig. 2. A: representative protein products of Fas ligand, Fas receptor, tumor necrosis factor-alpha (TNF-α), TNF receptor 1, and Fas-associated death domain (FADD) extracted from the left ventricles of excised hearts in 3 sedentary WKY (WKY), 3 SHR, and 3 SHR-EX were measured by Western blotting analysis. The α-tubulin was used as an internal control. B: bars represent the relative fold changes of protein quantification relative to WKY group in Fas ligand, Fas receptor/α-tubulin, TNF-α, TNF receptor 1, and FADD/α-tubulin and mean values ± SE (n = 6 in each group). *$P < 0.05$, **$P < 0.01$, significant differences from WKY group. #P < 0.05, ##P < 0.01 significant differences between SHR group and SHR-EX group.
H&E staining. To investigate whether there were changes in cardiac architecture, we did a histopathological analysis of left ventricular tissue stained with H&E. After viewing ×400 magnified images, we found that the ventricular myocardium in the WKY group showed normal architecture with normal interstitial space, but abnormal myocardial architecture and the increased interstitial space were observed in the SHR group. These myocardial architecture abnormalities in the SHR-EX group were less than those in the SHR group (Fig. 1A).

TUNEL-positive apoptotic cells of cardiac tissues. To view the apoptotic activity in cardiac tissues, the apoptotic cells and total cells were measured by TUNEL assay and DAPI staining, respectively, in the hearts from the WKY, SHR, and SHR-EX groups. Viewing images magnified ×400, we observed that the left ventricles of the SHR groups stained with TUNEL assay had a greater number of TUNEL-positive cardiac cells than those in the WKY group. The number of TUNEL-positive cardiac cells was decreased in the SHR-EX group, compared with SHR group (Fig. 1, B and C).

Upstream components of cardiac Fas receptor-dependent apoptotic pathways. To investigate the upstream components of cardiac Fas receptor-dependent apoptotic signaling pathways in hypertensive rats after exercise training, we measured the protein levels of Fas-dependent apoptotic pathway in hearts excised from WKY, SHR, and SHR-EX groups. Compared with the WKY group, the protein levels of Fas ligand, Fas receptor, TNF-α, TNF receptor 1, and FADD were significantly increased in the SHR group (Fig. 2). The protein levels of t-Bid, BAK, BAD, BAX, and cytochrome c were significantly increased in the SHR group (Fig. 3). The protein levels of t-Bid, BAK, BAD, BAX, and cytochrome c in the SHR-EX group were significantly lower than those in the SHR group (Fig. 3), suggesting that exercise training prevents cardiac Fas-dependent apoptotic pathway on hypertensive hearts.

Upstream components of cardiac mitochondria-dependent apoptotic pathways. To investigate the upstream components of cardiac mitochondria-dependent apoptotic signaling pathways in hypertensive rats after exercise training, we measured the pro-apoptotic protein levels of mitochondria-dependent pathway in hearts excised from WKY, SHR, and SHR-EX groups. Compared with the WKY group, the protein levels of t-Bid, BAK, BAD, BAX, and cytochrome c were significantly increased in the SHR group (Fig. 3). The protein levels of t-Bid, BAK, BAD, BAX, and cytochrome c in the SHR-EX group were significantly lower than those in the SHR group (Fig. 3), suggesting that exercise training prevent cardiac mitochondria-dependent apoptotic pathway on hypertensive hearts.

Downstream components of cardiac Fas receptor- and mitochondria-dependent apoptotic pathways. To identify the downstream components of cardiac Fas receptor-dependent and mitochondria-dependent apoptotic pathways, the caspase-8, caspase-9, and caspase-3 were measured by Western blotting in the hearts excised from the WKY, SHR, and SHR-EX groups.
Pro-form of caspase-8, caspase-9, and caspase-3 were similar among the WKY, SHR, and SHR-EX groups. Compared with the WKY group, the protein products of activated caspase-8, activated caspase-9, and activated caspase-3 were increased in the SHR groups (Fig. 4). The protein level of activated caspase-8, activated caspase-9, and activated caspase-3 in the SHR-EX group were significantly lower than those in the SHR group (Fig. 4), suggesting that exercise training prevents downstreams of cardiac Fas-dependent and mitochondria-dependent apoptotic pathway on hypertensive hearts.

Cardiac pro-survival pathway. To investigate the components of cardiac IGF1R/PI3K/AKT survival pathway in hypertensive rats after exercise training, we measured the pro-survival relative protein expression in hearts excised from WKY, SHR, and SHR-EX groups. Compared with the WKY group, the protein levels of IGF1, IGF1 receptor, p-PI3K, and p-Akt were significantly decreased in the SHR group. However, cardiac PTEN, a negative regulator of the p-PI3K/Akt signaling pathway, was similar among WKY, SHR, and SHR-EX (Fig. 5). The protein levels of IGF1, IGF1 receptor, p-PI3K, and p-Akt in the SHR-EX group were significantly increased compared with those in the SHR group (Fig. 5), suggesting that exercise training enhanced IGF1-related pro-survival pathway on hypertensive hearts.

To identify the components of cardiac pro-survival Bcl-2 family-associated pathway in hypertensive rats after exercise training, the pro-survival protein expression level of Bcl-2 and p-BAD were measured by Western blotting in the hearts excised from WKY, SHR, and SHR-EX groups. Compared with the WKY group, the protein products of Bcl-2 and p-BAD were decreased in the SHR groups (Fig. 5). The protein level of Bcl-2 and p-BAD in the SHR-EX group were significantly higher than those in the SHR group (Fig. 5), suggesting that exercise training enhanced Bcl2 family-related pro-survival pathway on hypertensive hearts.

DISCUSSION

Major findings. Our main findings can be summarized as follows. 1) The myocardial architecture in hypertensive rats became better after exercise training. 2) The two major apoptotic pathways in hypertensive hearts were significantly decreased after 3 mo of exercise training, the evidence for which is based on decreases of Fas receptor-dependent apoptotic proteins (Fas ligand, Fas receptor, TNF-α, TNF receptor 1, FADD, activated caspase-8, and activated caspase-3) and mitochondria-dependent apoptotic proteins (t-Bid, BAK, BAD, BAX, and cytochrome c, activated caspase-9 activated caspase-3) in the exercise training group compared with the sedentary hypertensive group. 3) The activity of the pro-survival pathway in hypertensive hearts was significantly increased after exercise training, the evidence for which is based on increases in IGF1, IGF1 receptor, p-PI3K, p-Akt, Bcl-2, and p-BAD in the exercise group compared with the sedentary hypertensive group. After integrating our current findings into previously proposed apoptotic theories, we draw a hypothe-

Fig. 4. A: representative protein products of caspase-8, -9, and -3 extracted from the left ventricles of excised hearts in 3 sedentary WKY, 3 SHR, and 3 SHR-EX were measured by Western blotting analysis. The α-tubulin was used as an internal control. B: bars represent the relative fold changes of protein quantification relative to WKY group in active caspase-8, active caspase-9, and active caspase-3/α-tubulin and mean values ± SD (n = 6 in each group). *P < 0.05, **P < 0.01, significant differences from WKY group. #P < 0.05, ###P < 0.01 significant differences between SHR group and SHR-EX group.

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sized diagram in Fig. 6, which suggests that cardiac Fas receptor-dependent and mitochondria-dependent pathways were increased in hypertension and suppressed by exercise training. In contrast, cardiac survival pathway was decreased in hypertension and was upregulated by exercise training. Our findings demonstrate new therapeutic effects of exercise training on hypertensive heart for preventing apoptosis and enhancing survival.

Exercise training has been known to provide multiple benefits such as anti-hypertension, anti-diabetes, anti-obesity, and anti-lipidemia (21). Cardiovascular benefits of exercise training in hypertensive patients may be improved by multiple factors such as cardiac function, cardiac output, decreased sympathetic activity, and increased capillary supply (8, 27). Therefore, any effect of exercise training on cardiomyopathic changes and cardiac apoptosis noted in the current study cannot be isolated and attributed to any specific factor, such as weight loss, blood pressure changes, or other unclear factors. The current study did differentiate new therapeutic effects of exercise training on cardiac apoptosis, but it did not prove cause-effect why exercise training protects against apoptosis.

Chronic hypertension is a major risk factor for the development of cardiovascular diseases (26). Hypertension induces pathological cardiac hypertrophy secondary to the pressure overload, thereby contributing to a decreased cardiac function and an increased cardiac apoptosis (6, 7, 19). The enlarged hypertrophic heart may gradually develop heart failure in both hypertensive humans and rats (12, 19). In previous studies, exercise training has been shown to protect the myocardium dysfunction and induce cardioprotection in cardiovascular diseases (16, 24). The current study showed that exercise training improved myocardial structure in the hypertensive heart.

The balance between cell death and cell survival is a tightly controlled process, especially in terminally differentiated cells, such as the cardiomyocytes (7). The Fas receptor-dependent apoptotic pathway is mediated by Fas ligand, Fas receptor, TNF-α, TNF receptor 1, FADD, and activation of caspase-8 (3, 9). In the current study, exercise training was found to signifi-
components were activated after exercise training. The evidence is based on hypertension-associated increases in Fas-dependent apoptotic pathway (TNF-α, TNF R1, Fas ligand (Fas L), Fas, FADD, activated caspase-8, and activated caspase-3) and the mitochondria-dependent apoptotic pathway (t-Bid, BAK, BAD, BAX, cytochrome c, activated caspase-9, and activated caspase-3) as well as those components that were not activated after exercise training. In contrast, cardiac pro-survival pathways become less activated in hypertension but become activated after exercise training. The evidence is based on hypertension-associated decreases in pro-survival pathway (IGF1, IGF1R, p-PI3K, p-Akt, Bcl2, and Bcl2) and those components were activated after exercise training.

The mitochondria-dependent apoptotic pathway is mediated by t-Bid, Bad, Bak, Bax, cytochrome c, activated caspase-9, and activated caspase-3 (3). In the current study, exercise training was found to significantly prevent more activated mitochondria-dependent apoptotic pathways observed in sedentary hypertension, as evidenced by decreases in hypertension-upregulated Fas ligand, Fas receptor, TNF-α, TNF receptor 1, FADD, activated caspase-8, and activated caspase-3 levels in rat hearts after exercise training. The current study is the first to report the prevention of cardiac Fas receptor-dependent apoptotic pathways.

We show some new findings of mitochondria-dependent apoptotic pathways observed in sedentary hypertension, as evidenced by decreases in hypertension-upregulated components of t-Bid, Bad, Bak, Bax, cytochrome c, activated caspase-9 levels, and activated caspase-3 levels after exercise training. From literature review, only one previous study has shown that exercise training reduced Bak and caspase-9 and increased Bcl-2 in hypertensive rats (11). We show some new findings of mitochondria-dependent apoptotic pathways such as t-Bid, Bad, cytochrome c, activated caspase-9 in hypertension after exercise training. Therefore, our findings strongly suggest that exercise training in hypertension could prevent cardiac apoptotic pathways. Because cardiomyocytes are terminally differentiated cells (7), the preventive effects of exercise training on cardiac apoptosis and cardiac cell death in heart health are very critical issues in hypertension-associated heart diseases.

Cardiac survival pathway can be mediated by IGF-related survival pathways, such as IGF1, IGF1 receptor, p-PI3K, and p-Akt, as well as Bcl2 family-related pro-survival pathways, such as Bcl-2 and p-BAD. In the current study, exercise training was found to significantly enhance cardiac survival pathway in hypertensive rats, the evidence for which is based on the increases in IGF1, IGF1 receptor, p-PI3K, p-Akt, Bcl2, and p-BAD after exercise training. The current study is the first to report IGF-related pro-survival effects of exercise training on hypertensive hearts.

Perspectives. Hypertension is considered to be a major risk factor for the development of heart failure, even when other known risk factors for heart failure are excluded. Because cardiac tissues are difficult to extract from hypertensive human hearts, the current hypertensive animal model under exercise training should provide an important explanation on how clinical exercise training prescription prevents heart failure or apoptosis-related cardiac diseases in hypertensive humans. Because hypertension will enhance cardiac apoptosis and exercise training can prevent this progression, people with long-term hypertension should be aware of the possibility of progressive development in cardiac abnormality and should devote themselves to exercise training and lifestyle modification. On the basis of the current evidence from the animal study showing that exercise training did prevent the major apoptotic pathways and enhance cardiac pro-survival pathways in hypertensive rats, we might further hypothesize that exercise training is a therapeutic agent for preventing cardiac apoptosis in hypertensive diseases. In addition, further questions are raised regarding what exercise training intensity, exercise training duration, and exercise training frequency will maximize the effects of anti-apoptosis in hypertension. Of course, further clinical studies are required to clarify the possible therapeutic application in hypertensive humans.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

EXERCISE AND CARDIAC APOPTOSIS


REFERENCES


