Exercise training improves systolic function in hypertensive myocardium

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Exercise training improves systolic function in hypertensive myocardium. J Appl Physiol 111: 1637–1643, 2011. First published September 15, 2011; doi:10.1152/japplphysiol.00292.2011.—The general purpose of this study was to test the effect of exercise training on the left ventricular (LV) pressure-volume relationship (LV/PV) and apoptotic signaling markers in normotensive and hypertensive hearts. Four-month-old female normotensive Wistar-Kyoto rats (WKY; n = 37) and spontaneously hypertensive rats (SHR; n = 38) were assigned to a sedentary (WKY-SED, n = 21; SHR-SED, n = 19) or treadmill-trained (WKY-TRD, n = 16; SHR-TRD, n = 19) group (~60% \(V\text{O}_2\) peak, 60 min/day, 5 days/wk, 12 wk). Ex vivo LV/PV were established in isovolumic Langendorff-perfused hearts, and LV levels of Akt, phosphorylated Akt (AktPi), Bad, phosphorylated Bad (BadPi) c-IAP, x-IAP, calcineurin, and caspases 3, 8, and 9 were measured. Heart-to-body weight ratio was increased in SHR vs. WKY (P < 0.05), concomitant with increased calcineurin mRNA (P < 0.05). There was a rightward shift in the LV/PV (P < 0.05) and a reduction in systolic elastance (Es) in SHR vs. WKY. Exercise training corrected Es in SHR (P < 0.05) but had no effect on the LV/PV in WKY. Caspase 3 was increased in SHR-SED relative to WKY-SED, while Bad, c-IAP, and x-IAP were significantly lower in SHR relative to WKY (P < 0.05). Exercise training increased Bad in both WKY and SHR but did not alter caspase 9 activity in either group. While caspase 3 activity was increased with training in WKY (P < 0.05), it was unchanged with training in SHR. We conclude that moderate levels of regular aerobic exercise attenuate systolic dysfunction early in the compensatory phase of hypertrophy, and that a differential phenotypic response to moderate-intensity exercise exists between WKY and SHR.

Aerobic exercise; blood pressure; cardiovascular disease; heart hypertension is a significant health concern as an independent risk factor for cardiovascular disease and as a precursor to heart failure (5). The hemodynamic overload presented by hypertension results in a maladaptive, pathological pattern of concentric cardiac hypertrophy and an increased rate of cardiomyocyte apoptosis (20, 26). Along these lines, cardiomyocyte apoptosis, autophagy, and necrosis are all thought to contribute to the progression of heart failure through distinct individual and shared signaling pathways (36–38). Our laboratory has consistently reported that chronic aerobic exercise training augments cardiac remodeling in the spontaneously hypertensive rat (SHR) model (25, 26, 33, 39, 41, 42). Our studies indicate that training increases cardiomyocyte hypertrophy and cardiomyocyte proliferation, while attenuating TUNEL-positive (TUNELpos) cardiomyocytes in SHR myocardium (26). These data have led us to hypothesize that exercise training improves the overall cardiomyocyte balance in hypertensive hearts and may be a beneficial mechanism in delaying the development of heart failure (4, 13, 27, 32). Given that training-induced reductions in apoptosis might be central in maintaining cardiomyocyte number, we hypothesized that training would improve the intrinsic, antiapoptotic profile of hypertensive hearts. We also sought to determine whether moderate-intensity training induced a differential adaptive response between normotensive and hypertensive hearts.

One pathway associated with apoptosis is the intrinsic or mitochondrial death pathway. Via action on the mitochondrial membrane, proapoptotic members of the Bcl-2 family of proteins, e.g., Bad, destabilize the mitochondrial membrane, triggering the release of cytochrome c (2, 8, 40). Cytochrome c release and subsequent apoptosis formation result in the activation of initiator caspase 9, activation of downstream executioner caspases, and cell death. Through the phosphorylation of key components of the mitochondrial death pathway or through alterations in gene expression of cell death machinery, protein kinase B (Akt) has emerged as a key regulator of cell survival (8). Akt-mediated phosphorylation of Bad promotes cell survival by decreasing mitochondrial membrane destabilization and cytochrome c release (8, 9, 23). Furthermore, Akt is capable of directly phosphorylating caspase 9, thereby decreasing its catalytic ability (3). Given that phosphatidylinositol 3-kinase (PI3K)/Akt pathway has been shown to be centrally related to the development of exercise-induced physiological hypertrophy (34), we tested whether chronic aerobic training altered the protein abundance of Akt and Bad and their respective levels of phosphorylation in normotensive and hypertensive hearts. We also established whether training altered cardiac performance to a Starling challenge in normotensive and hypertensive hearts. The Wistar-Kyoto rat (WKY) and SHR models were utilized for these experiments on the basis that SHR mimic well the clinical course of untreated essential hypertension in humans and are well documented to show left ventricular (LV) chamber enlargement by 6–12 mo of age (1, 6, 11, 16, 24).

METHODS

Experimental paradigm. Seventy-five 4-mo-old female WKY (n = 37) and SHR (n = 38) animals were obtained from Charles River Laboratories (St-Constant, QC, Canada). Animals from each group were randomly stratified into sedentary (WKY-SED, n = 21; SHR-SED, n = 19), or exercise-trained (WKY-TRD, n = 16; SHR-TRD, n = 19) groups. All rats were housed three per cage, maintained on a 12:12-h light-dark cycle, and fed ad libitum (Harlan Teklad Global Diets, 18% Protein Diet, Madison, WI). Exercise consisted of moderate-intensity endurance training at a speed of 25 m/min, 0% grade, 60 consecutive min/day, 5 days/wk for a period of 12 wk (25, 26, 33, 39, 41, 42). We have previously shown that this training paradigm significantly increases soleus citrate synthase activity in SHR (25).
Also, we have shown that the identical protocol enhances myocyte length and width in hypertensive hearts (26). To account for handling and noise-induced stress, both WKY-SED and SHR-SED were placed near the treadmill during exercise sessions. Blood pressure and heart rate (HR) were collected prior to death with a tail-cuff apparatus (Kent Scientific, Torrington, CT, XBP 1000) (33). Animals were acclimatized to the tail cuff apparatus two times prior to blood pressure determination. Fifty-one animals were killed at 7 mo of age for ex vivo LV functional studies (WKY-SED, n = 15; WKY-TRD, n = 10; SHR-SED, n = 13; SHR-TRD, n = 13), while hearts from the remaining animals (n = 6/group) were used for caspase measurements and Western blots. All animals received humane care according to protocols reviewed and approved by the University Institutional Animal Care and Use Committee and in compliance with the “Principles of Laboratory Animal Care” formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Pub. No. 85-23, revised 1985).

**Langendorff experiments.** To determine the effects of exercise on LV mechanical function, LV pressure-volume relationships were determined in isolated, isovolumic buffer-perfused hearts. Rats were anesthetized with pentobarbital sodium (60 mg/kg ip) and heparinized (500 U iv). A thoracotomy was performed, and the heart was excised and then perfused retrograde with a Langendorff apparatus as previously described (39, 41, 42). During equilibration, all hearts were loaded with an initial balloon volume yielding an LV end-diastolic pressure (LVEDP) of 10 mmHg. LV systolic pressure (LVSP), LVEDP, and coronary perfusion pressure (CPP) were continuously recorded by means of a data acquisition system (Powerlab/8SP, ADI Instruments, Colorado Springs, CO). LV developed pressure (LVdevP) was calculated by subtracting LVEDP from LVSP. Hearts were paced at 5 Hz (Grass Instruments, Quincy, MA) and immersed in a water-jacketed organ chamber at 37°C throughout the protocol.

**Left ventricular pressure-volume relationship.** After 20 min of equilibration, the LV pressure-volume relationship was established over a wide range of LV filling volumes as previously described (31, 42). Briefly, with a Hamilton syringe, LV balloon volume was increased in 5- to 10-μl increments until an LVEDP of 42. Briefly, with a Hamilton syringe, LV balloon volume was increased in 5- to 10-μl increments until an LVEDP of 30 mmHg was achieved. To compare the LV pressure-volume relationship between groups, LV volumes were determined from each pressure-volume curve at 5-mmHg intervals (31). The LVSP-volume relationship (LVSP/V) and the LVEDP-volume relationship (LVEDP/V) were curve fit with a best fit analysis, with the linear slope of the LVSP/V indicating the systolic elastance (Es). The slope of the LVEDP/V relationship was used to reflect the LV diastolic chamber stiffness. LV capacitance (V_{25}) was measured as the LV volume that elicited an LVEDP of 25 mmHg.

**Protein assay/Western blot analysis.** Frozen tissue was weighed and homogenized on ice in PBS lysis buffer containing 2% sodium dodecyl sulfate (SDS; FisherBiotech), 1% IGEPA CA-630 (Sigma), 0.5% deoxycholate (Sigma), 5 mM EDTA, and proteinase inhibitors (aprotinin, leupeptin, 1 mM phenylmethylsulfonyl fluoride, and pepstatin A, calpain inhibitor I and II, and benzamidine). Tissue protein abundance and phosphorylation levels in isolated protein [Akt, phosphorylated Akt (Aktπ), Bad, phosphorylated Bad (Badπ) c-IAP, and x-IAP] were analyzed by Western blot analysis. Target antigens were probed with phosphorylation-specific polyclonal antibodies for Akt and Bad. Blots were measured with densitometry using Image J software (National Institutes of Health).

**Caspase activity assay.** The tissue was washed with PBS and scraped off in ice-cold lysis buffer provided with caspase assay kits used to detect caspases 3, 8, and 9 (EMD Biosciences). After sonication, the lysate was centrifuged for 20 min at 14,000g at 4°C. The supernatants were analyzed for protein content and used for caspase colorimetric enzymatic activity assays per the manufacturer’s instructions with 96-well plates. Absorbance was recorded on a plate reader immediately after the start of the assay and after 10–16 h of incubation at 37°C. The net increase in absorbance represented enzyme activity.

**RT-PCR mRNA.** Calcineurin A mRNA expression was assessed by RT-PCR. Calcineurin primers were 5’-CCACAGGAGTGGTTGCTG (forward) and 5’-GTCCCGTGTTTCACTGTGGTA (reverse). RT-PCR reactions were performed along with 1 μg of cDNA created from RNA with iScript (Bio-Rad) followed by 22 cycles of PCR amplification (amplification temperature 62.5°C) with a Bio-Rad iCycler. Appropriate melt curves were also run. Individual samples were normalized to levels of 28S: 5’-TGGAAA-ATCCGGGGGAGAG (forward) and 5’-ACATTGTCACACAGGCCAG (reverse) with group differences (RQ) expressed relative to an individual animal from the WKY-SED group.

**Data analysis and interpretation.** In vivo hemodynamics, animal characteristics, LVEDP/V, LVSP/V, LV capacitance, diastolic slope, peak and relative LVdevP, CPP, and molecular analyses were compared with 2 × 2 ANOVA (hypertension vs. exercise main effects) followed by Tukey post hoc analysis when appropriate. All analyses were performed with SPSS version 15.0 (SPSS, Chicago, IL). Statistical significance was set at an α level of P < 0.05. All data are reported as means ± SE.

### RESULTS

#### Hemodynamic parameters and animal characteristics.**

Table 1 illustrates the systolic blood pressure (SBP), heart rate (HR), and rate-pressure product (RPP) in WKY and SHR animals at 7 mo of age. Significant differences between WKY and SHR existed for SBP, HR, and RPP (main effects; P < 0.05). Exercise training also significantly reduced both HR and RPP in SHR-TRD compared with SHR-SED animals (P < 0.05). SBP, HR, and RPP were similar in WKY-SED and WKY-TRD animals.

The physical characteristics of the experimental groups are presented in Table 2. Prior to death, body weight was lower in SHR versus WKY (main effect; P < 0.05). Tibial length was greater in TRD versus SED (treatment effect; P < 0.05), and heart weight-to-body weight ratio was increased in SHR relative to WKY (main effect; P < 0.05). There were no differences for heart weight or heart weight-to-tibial length ratio among groups.

<table>
<thead>
<tr>
<th></th>
<th>WKY-SED</th>
<th>WKY-TRD</th>
<th>SHR-SED</th>
<th>SHR-TRD</th>
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<tbody>
<tr>
<td>SBP, mmHg</td>
<td>141 ± 3</td>
<td>146 ± 6</td>
<td>180 ± 2*</td>
<td>175 ± 3*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>389 ± 7</td>
<td>377 ± 12</td>
<td>503 ± 6*</td>
<td>454 ± 10*†</td>
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<td>RPP</td>
<td>54,857 ± 1,643</td>
<td>55,607 ± 3,655</td>
<td>90,340 ± 1,477*</td>
<td>79,055 ± 2,759†</td>
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</table>

Data are presented as means ± SE. WKY, Wistar-Kyoto rat; SHR, spontaneously hypertensive rat; SED, sedentary; TRD, trained; SBP, systolic blood pressure; HR, heart rate; RPP, rate-pressure product. *Main effect for WKY vs. SHR; †P < 0.01 vs. SHR-SED.

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**Table 1. In vivo hemodynamics**
**Table 2. Physical characteristics**

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<thead>
<tr>
<th></th>
<th>WKY-SED</th>
<th>WKY-TRD</th>
<th>SHR-SED</th>
<th>SHR-TRD</th>
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<tbody>
<tr>
<td>Body weight, g</td>
<td>232 ± 5</td>
<td>250 ± 6</td>
<td>209 ± 4*</td>
<td>217 ± 5*</td>
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<tr>
<td>Heart weight, g</td>
<td>1.05 ± 0.04</td>
<td>1.09 ± 0.03</td>
<td>1.09 ± 0.04</td>
<td>1.15 ± 0.04</td>
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<tr>
<td>Tibial length, cm</td>
<td>3.56 ± 0.03</td>
<td>3.70 ± 0.04*</td>
<td>3.63 ± 0.04</td>
<td>3.64 ± 0.05†</td>
</tr>
<tr>
<td>HW/BW, mg/g</td>
<td>4.54 ± 0.16</td>
<td>4.37 ± 0.13</td>
<td>5.23 ± 0.15*</td>
<td>5.31 ± 0.12*</td>
</tr>
<tr>
<td>HW/TL, g/cm</td>
<td>0.30 ± 0.01</td>
<td>0.29 ± 0.01</td>
<td>0.30 ± 0.01</td>
<td>0.32 ± 0.01</td>
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Data are presented as means ± SE. HW/BW, heart-to-body weight ratio; HW/TL, heart-to-tibial length ratio. *P < 0.05 main effect WKY vs. SHR; †P < 0.05 main effect SED vs. TRD.

Langendorff isolated heart performance. Figure 1 illustrates the pressure-volume relationships in both WKY and SHR animals. The LVEDP/V was shifted slightly rightward in SHR relative to WKY (main effect; P < 0.05) but was not statistically different between TRD and SED. There was also an increased LV capacitance (main treatment effect; P < 0.05) in SHR relative to WKY (WKY-SED: 55 ± 6 μl, WKY-TRD: 56 ± 4 μl, SHR-SED: 75 ± 4 μl, SHR-TRD: 66 ± 8 μl), with no differences in LV diastolic chamber stiffness among groups. As Fig. 2 illustrates, the slope of the LVSP/V, i.e., E_s, was depressed in SHR relative to WKY (main effect and interaction; P < 0.05) but was increased with training in SHR-TRD vs. SHR-SED (P < 0.05). We also measured CPP at an LVEDP of 10 mmHg as a marker of coronary resistance. CPP was greater in SHR relative to WKY (main effect; P < 0.05)

**Fig. 2.** E_s in WKY and SHR. E_s was depressed in SHR relative to WKY (main effect; P < 0.05) but improved with training in SHR (P < 0.05). Data are presented as means ± SE. *P < 0.05 for SHR-SED vs. SHR-TRD.

(WKY-SED: 82 ± 3 mmHg, WKY-TRD: 100 ± 6 mmHg, SHR-SED: 126 ± 9 mmHg, SHR-TRD: 95 ± 4 mmHg), illustrating greater coronary resistance with hypertension.

**Apoptotic markers and caspases.** As Fig. 3A illustrates, the abundance of Akt was greatest in SHR-SED relative to the other groups (P < 0.05; following a significant interaction effect), despite no significant differences in AktD (Fig. 3B). The abundance of Bad was not different (Fig. 3C) across groups, while Badp was greater in WKY versus SHR (main effect; P < 0.05) and increased with training in both WKY and SHR (P < 0.05; following a significant main effect) (Fig. 3D). Both c-IAP and x-IAP were lower in SHR relative to WKY hearts (main effect; P < 0.05), with no training effect induced for either marker (Fig. 3, E and F). Calcineurin mRNA was significantly increased in SHR-SED (P < 0.05; following a significant interaction effect) and mitigated with training in SHR-TRD (Fig. 4). Table 3 summarizes caspase 3, 8, and 9 activities in our study sample. Caspase 3 activity was significantly lower in WKY-SED versus WKY-TRD and SHR-SED (P < 0.05; following a significant interaction effect). There were no significant treatment or training effects for caspase 8 or 9 among groups.

**DISCUSSION**

In this study, we found an impaired E_s, increased calcineurin mRNA, decreased antiapoptotic protein abundance, and increased caspase 3 activity in hearts harvested from sedentary SHR relative to WKY. We also found that exercise training improved E_s and decreased calcineurin mRNA in SHR but not in WKY. While exercise improved Bad phosphorylation in both SHR and WKY, it did not translate into a lower caspase 9 or 3 activity in either strain. In fact, moderate-intensity exercise increased caspase 3 activity in WKY-TRD relative to WKY-SED, without altering the pressure-volume relationship in WKY. We conclude that 1) moderate levels of regular treadmill exercise attenuate systolic dysfunction early in the compensatory phase of hypertension-induced hypertrophy independent of lowering caspase 3 activity and 2) a differential apoptotic and functional phenotypical response to moderate-intensity exercise exists between WKY and SHR.

Apoptosis is an important component of pathological cardiac remodeling and is central in the pathogenesis of heart failure.
Apoptosis has been reported to be increased in the LV of young, adult, and senescent SHR (1, 11, 15, 26) as well as in other models of pressure overload (7, 18). Results of the present study are in accord with these previous reports. Morphological alterations such as cell shrinkage, membrane blebbing, DNA fragmentation, and chromatin condensation (10, 36–37) are typical features of apoptotic cardiomyocytes. Apoptosis may be induced either by a death ligand (extrinsic pathway) or by mitochondrion-related mechanisms (intrinsic pathway) (10) and is triggered by a host of cues, including reactive oxygen species, elevated intracellular Ca²⁺ concentration, and tumor necrosis factor.

In the present study, we focused our attention on the role that training exerts on the intrinsic apoptotic pathway, because of previous published reports showing that PI3K/Akt signaling is upregulated with training (34). Through the phosphorylation of key components of the mitochondrial death pathway or through alterations in gene expression of cell death machinery, Akt is appreciated as a key regulator of cell survival (8). Akt-mediated phosphorylation of Bad prevents the inactivation of pro-survival factors, thereby promoting cell survival by decreasing mitochondrial membrane destabilization and cytochrome c release (8, 9, 23). Furthermore, Akt is capable of directly phosphorylating caspase 9, thereby decreasing its catalytic ability (3). Here we report that despite similarities in phosphorylated Akt, the level of phosphorylated Bad (i.e., inactivated Bad) was significantly greater in WKY compared with SHR. Moreover, treadmill training increased Bad phosphorylation in both WKY and SHR without altering caspase 9 activity in either strain. These observations may suggest that other protein kinases, such as protein kinase C, or phosphatases such as calcineurin mediate Bad phosphorylation and that Bad phosphorylation in and of itself does not translate into an attenuation of caspase 9 activity.

Calcineurin, a Ca²⁺/calmodulin-dependent protein phosphatase, has been reported to oppose Akt-mediated phosphorylation of Bad (43, 51) and is reproducibly increased in pressure-overload hypertrophy (35). In the present study, we report that training mitigated gene expression of calcineurin in

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<th>Table 3. Myocardial caspases</th>
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<tr>
<td>Caspase 3</td>
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<td>Caspase 8</td>
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<td>Caspase 9</td>
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Data (in rfu·min⁻¹·mg⁻¹) are presented as means ± SE. *P < 0.05 vs. WKY-TRD and SHR-SED. rfu, relative fluorescence units.
SHR. These results are consistent with our previous work showing that calcineurin protein abundance and activity were increased in SHR (26) and reduced in SHR animals undergoing 3 mo of treadmill training (26). Thus a plausible mechanism for increased Bad phosphorylation in SHR may be a training-induced mitigation of calcineurin. However, Bad phosphorylation was also elevated in WKY with training, without a training effect on calcineurin, suggesting the involvement of other regulatory factors.

While the phosphorylation of Bad is likely to mitigate downstream activation of proteolytic caspases, the catalytic potential of these caspases can also be regulated directly by a family of proteins called the inhibitors of apoptosis (IAPs) (44). Of the IAPs, x-IAP is the best characterized and appears to directly inhibit the catalytic ability of caspase 9 (50). c-IAP is also an antiapoptotic molecule capable of binding caspase 9 and inhibiting caspase 3 (12, 45). In the present investigation, the abundance of c-IAP and x-IAP were decreased in SHR relative to WKY without any training effect for either protein. The reduction of c-IAP and x-IAP in SHR is also consistent with the increased caspase 3 activity observed in SHR-SED relative to WKY-SED.

Our finding of greater caspase 3 activity in WKY-TRD relative to WKY-SED is of interest, given that several previous reports have shown that exercise training attenuates apoptosis in normotensive rodent myocardium (19, 28, 48, 49). Moreover, previous studies on pressure overload have also reported a reduction in various antiapoptotic markers following training (26, 29, 30). In the present study, caspase 3 was similar between SHR-SED and SHR-TRD. While we previously reported that exercise training reduced TUNELpos cardiomyocytes in SHR myocardium (26), we do not view the lack of a training effect on caspase 3 activity in SHR in the present study as contradictory with these previous findings. Measurement of caspase 3 activity is temporally indicative of only one point in time, whereas the number of TUNELpos cardiomyocytes is summative. Moreover, TUNELpos cells reflect broken DNA strands and are not specific for apoptosis exclusively. Thus other modes of cell death, e.g., necrosis, can also yield TUNELpos cardiomyocytes and factor into regulating cardiomyocyte number in hypertension. Additional experimental paradigm variations in animal strain, sex, training status, and age also factor into differences related to exercise in various reports across the literature. Clearly, the impact of exercise on myocardial apoptosis requires further study, particularly with respect to its specific regulatory role on cardiac function.

Systolic cardiac function has been shown to be altered in SHR, with some reports showing systolic function to be decreased (24, 42), increased (6), or unchanged (47) early in the course of hypertension. In the present study, E, was significantly lower in SHR compared with WKY. These results are directionally consistent with our previous report of a decreased absolute E, in older SHR hearts compared with WKY (42). Taken together, these data suggest that a blunted Starling response occurs very early in the development of compensatory hypertrophy. The Starling relationship is predicated on the influence of myofiber length on myofilament activation, a process known as length-dependent activation (14). Both optical actin-myosin overlap and increased myofilament calcium responsiveness are thought to mechanistically explain this effect (17). Moreover, cardiomyocyte activation number, which is attenuated with apoptosis in hypertension, may play a role. Apoptotic cardiomyocyte loss is associated with a progressive decline in LV function and heart failure (36–38). In the present study, exercise lessened the decline in E, in SHR but did so independently of reducing caspase 3 activity. These data suggest that the favorable functional profile observed in trained SHR hearts was not secondary to an attenuation of apoptosis.

In conclusion, our study shows that systolic dysfunction occurs very early in the compensatory phase of pressure-overload hypertrophy, without evidence of diastolic dysfunction. Consistent with other studies, increased apoptosis appears to be associated with the impaired systolic function in hypertensive hearts. While moderate levels of regular exercise attenuated systolic dysfunction early in the compensatory phase pressure-overload hypertrophy, the effect appears independent of mitigating apoptosis. Moderate-intensity exercise did not improve the Starling response in normotensive hearts, suggesting that a differential phenotypical response to exercise exists between normotensive and hypertensive rodent myocardium. More work exploring varying intensities and durations of exercise training on apoptosis and function is needed.

REFERENCES


