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ORIGINAL ARTICLE

Interaction between exercise and hypertension in spontaneously hypertensive rats: a meta-analysis of experimental studies

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The effect of exercise on the progression of hypertension and development of heart failure has been extensively studied in spontaneously hypertensive rats (SHRs), but results published thus far have not revealed a clear picture. Studies differ with respect to the age and sex of rats, duration of exercise and exercise protocols. This study was aimed to examine the influence of age at the start of exercise and the effect of the duration of exercise on blood pressure and hypertrophy, which has not been previously investigated. We identified 18 reports in the literature (with a total of about 410 rats) that investigated the effect of exercise on SHR. A reduction in blood pressure was observed in rats that started exercise protocols in the pre-hypertensive or very early hypertensive state, but not in older rats. Exercise lowered the heart weight-to-body weight ratio in rats starting exercise at a very early age, but not in rats at an advanced age. A reduction in blood pressure was observed in animals that had a short period of training, but the effect was lost when the duration of exercise was prolonged. Exercise reduced resting heart rates in all groups and increased the heart weight-to-body weight ratio in groups that were exposed to free running wheels, but not in rats that performed treadmill exercise. In conclusion, exercise *per se* does not reduce blood pressure in SHR with established hypertension and may increase the incidence of myocardial hypertrophy, depending on the form of exercise.
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Keywords: blood pressure; exercise; hypertrophy

INTRODUCTION

Treatment of hypertension is considered a successful intervention to reduce cardiovascular risk. Multiple blood pressure-reducing pharmaceutical approaches are in clinical use. However, recommendations for changes in lifestyle are used as the first and most promising steps leading to a reduction in blood pressure, use of blood pressure-lowering medication, delay of end-organ damage and increased insulin sensitivity. These recommendations include cessation of smoking, reduction in fat and salt intake and increased physical activity.[1–3] Furthermore, endurance training has become very popular over recent years, but due to the high prevalence of unrecognized hypertension in the population engaged in endurance training, it may be associated with cardiac risk. In contrast to blood pressure medication, which is a treatment that has been established after successful animal experiments and extensive basic research, the benefits of physical activity for controlling blood pressure have been less well studied and there are fewer data available. This is regrettable because it is difficult to determine whether any observed benefit in patients is related to physical activity or to other lifestyle changes that are recommended in combination with exercise.[3] Of note, exercise activities add hemodynamic stress to the cardiovascular system and increase the risk of ischemic episodes.[4] Endurance exercise is considered to trigger an adaptive type of myocardial hypertrophy that differs in various aspects from the well-known compensatory hypertrophy caused by chronic hypertension. However, it is largely unknown how the heart reacts to the onset of exercise in the context of established structural and functional adaptations to hypertension.

Spontaneously hypertensive rats (SHRs) are an established and widely used hypertension model, and SHRs have been used to investigate the effect of exercise on the progression of hypertension in numerous studies. Beneficial effects that have been described are a decrease in oxidative stress,[5,6] an increase of cytochrome oxidase activity in cardiac mitochondria,[7] a fall in blood pressure,[8,9] normalization of calcium-handling proteins,[10,11] delayed hypertrophy-associated fetal gene shifts,[12] improvement of endothelium-dependent vasorelaxation,[13,14] induction of antiapoptotic genes[15,16] and improved β-adrenoceptor coupling.[17] In contrast, a normalization of calcium-handling proteins was not observed by others,[7] nor was a fall in blood pressure,[18] a change in the function of cardiomyocytes,[19] or a change in heart function.[20] Moreover, exercise resulted in greater fibrosis and adverse remodeling in another study.[21] Therefore, although numerous studies have been performed on SHR, these studies involved small numbers of animals, different exercise protocols, different durations of exercise and rats of different ages and

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groups of varying sex distribution. Therefore, key questions, such as the influence of age at the start of exercise and effects of the duration of exercise, have not been answered.

In order to address these questions, we performed a meta-analysis of animal studies dealing with the effect of exercise on hypertension. Using this approach, we were able to report on study results based on more than 400 rats. In this study, we describe the role of the animal's age at the start of exercise and the effect of the duration of exercise on blood pressure and hypertrophy in SHR. As pointed out above, these questions have not been addressed in individual studies.

METHODS

Literature

Studies were identified from the Medline database by a search with the keywords 'SHR' and 'exercise'. Studies were used for this analysis if they included a training group and a non-training group, which was usually denoted as sedentary (although this term might not be appropriate for animals that do not 'sit'). Studies selected for this analysis were only considered if they reported data about systolic blood pressure, heart rate and/or heart weight-to-body weight ratio. Furthermore, studies had to be published in English. The literature selected was published between 2002 and 2008.

Analysis

For further analysis of all studies, rats were grouped according to the age of the animals at the beginning of the experiments, at the start of the exercise program or according to the duration of the exercise protocol. Further details are given in the Results section.

Statistics

All data are expressed as means ± s.e. Comparisons between groups were performed by a *t*-test.

RESULTS

Study identification and description

A total of 17 studies published between 2002 and 2008 that fulfilled the criteria defined above were found (Table 1). In these studies, the age of rats at the beginning of the exercise treatment varied from 4 weeks (pre-hypertensive state) up to 16 weeks (established hypertension). Group sizes differed from n=5 to n=30 animals per study. Seven studies used female rats and 10 studies used male rats. In 16 studies, blood pressure was measured by a tail-cuff approach. Three studies compared blood pressure measurement by the tail-cuff method with direct measurement in anesthetized rats. In two of them, blood pressure was significantly higher when measured by the tail-cuff method (182 *vs.* 126 mm Hg and 189 *vs.* 126 mm Hg),[18,20] and no significant differences were found in the third study (179 *vs.* 188 mm Hg).[16] For that reason, only studies in which blood pressure was recorded by the tail-cuff method were included in the analysis of blood pressure. In 14 studies, a treadmill protocol was used. According to this protocol, rats were trained 5 days per week on average, at a mean rate of 19 m/min, accounting for a total running distance of 5.5 km per week. Two studies used a free running wheel model, in which the rats ran 41.1 km per week on average. Finally, one study used a swimming protocol (Table 1).

Table 1 Studies included in the meta-analysis and study details

Ref	*Age (months)*	*Sex*	n	*Training*
13	3	m	12	1.5 months, treadmill
14	1	m	30	2.5 months, free running
15	1.5	m	15	3 months, treadmill
16	1	m	6–8	2 months, treadmill
17	4	f	12	3 months, treadmill, low intensity
18	2–3	f	11	13 weeks, treadmill, low intensity
20	4	f	7–8	6 months, treadmill, low intensity
22	1	m	20–21	2.5 months, free running
23	1.5	m	6	2 months, swimming
24	1.5	m	5	5 months, treadmill
25	2	m	8	3 months, treadmill, low intensity
26	2	m	9	3 months, treadmill
27	2	f	12	3 months, treadmill
28	3	m	12	2.5 months, treadmill
29	4	f	9–10	4 months, treadmill low intensity
30	4	f	11–12	6 months, treadmill, low intensity
31	4	f	7–8	3 months, treadmill, low intensity
12[a]	9/15	m	9–10	6 months, treadmill
21[a]	6	f	11–12	16 months, free running

Abbreviations: f, females; m, males; n, number of animals per group; SHHF, spontaneously hypertensive heart failure.
[a]SHHF (only used for hypertrophy data).

Effect of exercise on blood pressure

Of the studies examined, 16 reported about the effect of exercise on systolic blood pressure. Animals used in these studies were between 1 and 4 months old. Rats in these studies were grouped according to their age at the beginning of exercise as follows: 1 month (3 studies),[14,16,22] 1.5 months (3 studies),[15,23,24] 2–2.5 months (4 studies)[18,25–27] and 3–4 months (6 studies).[17,20,28–31] The number of rats included in these groups is depicted in Figure 1a. Exercise duration varied in these groups. There was a trend toward higher exercise duration in studies using older rats (Figure 1a). On average, rats starting with exercise at the age of 4 months were exposed to longer exercise protocols than those beginning at 1 month (Figure 1a). Values for mean systolic blood pressure among rats were 133.1, 142.5, 172.0 and 167.7 mm Hg at the ages of 1.0, 1.5, 2.3 and 4.0 months, respectively. A blood pressure-lowering effect was observed in studies using rats at the pre-hypertensive or early hypertensive stage, independent of exercise duration and intensity (Figure 1b). On average, systolic blood pressure was 13.6 ± 1.0 and 17.2 ± 0.9 mm Hg lower than that of sedentary controls in animals starting exercise at the ages of 1.0 and 1.5 months, respectively. Similarly, when the age of rats at the end of the exercise protocol was considered, younger rats had lower blood pressure compared with their sedentary counterparts (Figure 1c). These data suggest that a blood pressure-lowering effect can be expected only in young and pre-hypertensive rats but not in older rats with established hypertension. Indeed, when the duration of exercise was analyzed separately for young (mean age 1.3 months) and older (mean age 4.0 months) rats, a blood pressure-lowering effect was seen only in young rats (Figure 2). Eleven studies provided additional information about blood pressure before the start of exercise. Of note, in none of these studies did exercise reduce blood pressure. The mean blood pressure at the start of the exercise was 162.6 ± 8.3 mm Hg; at the end it was 182.4 ± 8.0 mm Hg.

Effect of exercise on heart rate

Seven studies reported on the effect of exercise on heart rate.[15,18,20,25,29,30,32] Again, in all these studies, rats started with exercise at the age of 1–4 months, and those that were older at the beginning had a longer exercise period. Studies were grouped as before on the basis of the different ages of the animals at the beginning of the study. Group statistics are given in Figure 3a. In all studies, resting heart rate was lower in rats performing exercise, irrespective of the age of the rat at the beginning or end of the exercise periods (Figure 3b

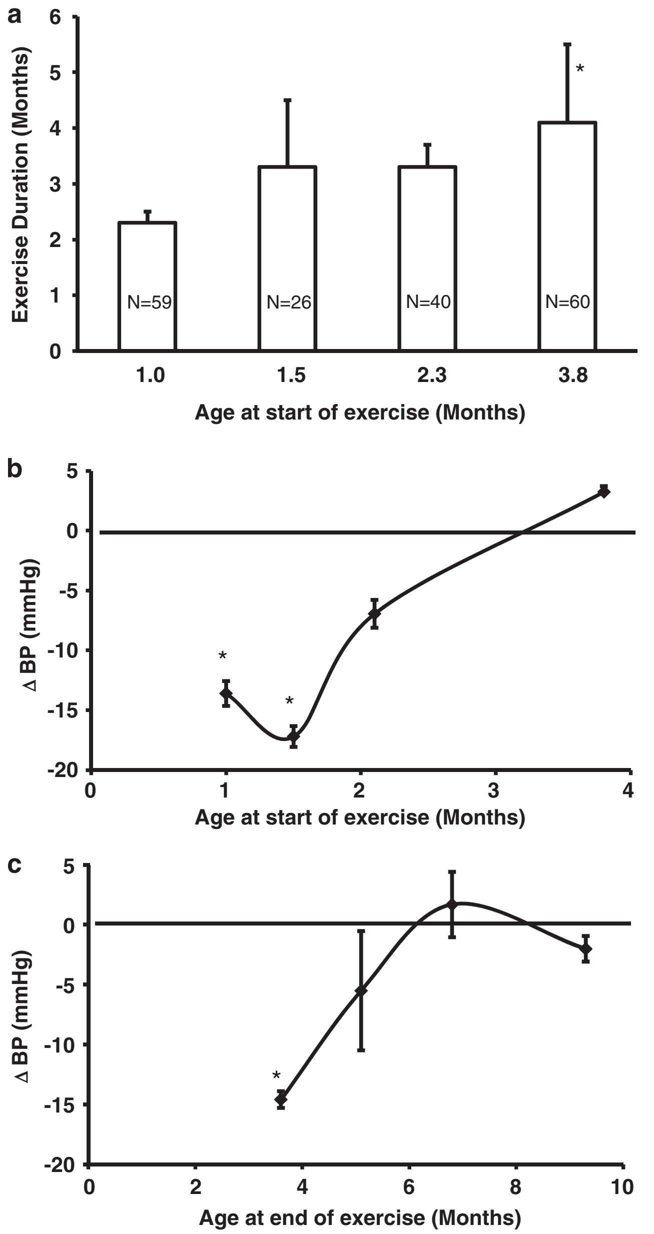

Figure 1 Effect of the age of animals on exercise-dependent changes in blood pressure. Animals were grouped according to their age at the beginning of the exercise training. (**a**) Bars represent the number of rats per group and indicate the mean exercise duration for each group. (**b**) Difference in blood pressure between rats performing exercise and their sedentary controls for the four groups defined above. (**c**) Difference in blood pressure between rats performing exercise and their sedentary controls for groups defined by similar age at the end of exercise. Data are means ± s.e.; $^*P<0.05$ *vs.* sedentary controls.

and c). There was a trend toward minor effects on heart rate if the animals were older, but whether this is a real physiological effect could not be discerned from these data.

Effect of exercise on heart weight-to-body weight ratio

Nine studies described the effect of moderate treadmill exercise or swimming on heart weight-to-body weight ratios. Two studies used young rats (1.5 months),[15,23] five studies used rats at an age between 3 and 4 months (mean of 3.8 months),[13,20,29–31] and two groups used

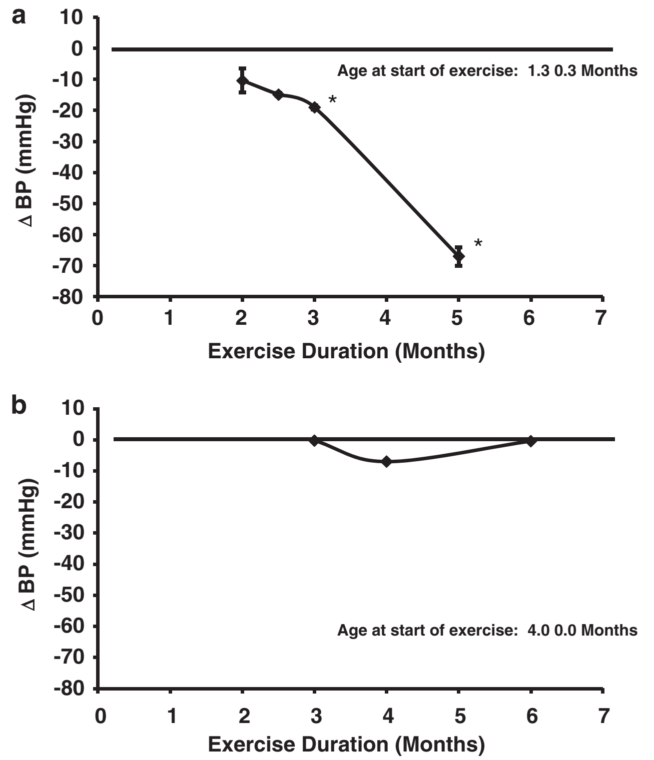

Figure 2 Effect of the age of spontaneously hypertensive rats (SHR) on changes in blood pressure during prolonged exercise. (**a**) Data are given for studies using rats at the age of 1.0–1.5 months. (**b**) Data are given for studies using rats at the age of 4 months. Data are means ± s.e.; $^*P<0.05$ *vs.* sedentary controls.

rats at an age between 9 and 15 months (12 months).[12] The latter study was performed on spontaneously hypertensive heart failure rats. We included these data because no data on SHR are available. Unlike SHR, all spontaneously hypertensive heart failures develop heart failure that can be characterized as decompensated dilated heart failure. Although they differ from SHR in their genetic background, we decided to include this group because no major differences in blood pressure or heart weight-to-body weight ratio were seen in the sedentary group compared with SHR. Group statistics are given in Figure 4a. Again, older rats were exposed to exercise periods that were longer in duration. Lower heart weight-to-body weight ratios were only reported in studies with young rats (Figure 4b and c). In older animals, there is a clear trend toward higher values. When the changes in heart weight-to-body weight ratio are plotted against the duration of exercise, it becomes evident that the antihypertrophic effect of exercise in these hypertensive rats may be a transient phenomenon (Figure 5).

Effect of the type of exercise on blood pressure and heart weight-to-body weight ratio

The data reported above were based on treadmills (with the exception of one group that performed a swimming protocol). There were significant differences in training intensity between rats performing treadmill exercise and those exposed to a free running protocol. Rats performing treadmill exercise had a weekly running distance of 5–8 km per week, but those with free access to running wheels ran between 35 and 47 km per week. This leads to the question of whether there are significant differences between these types of exercise. Studies

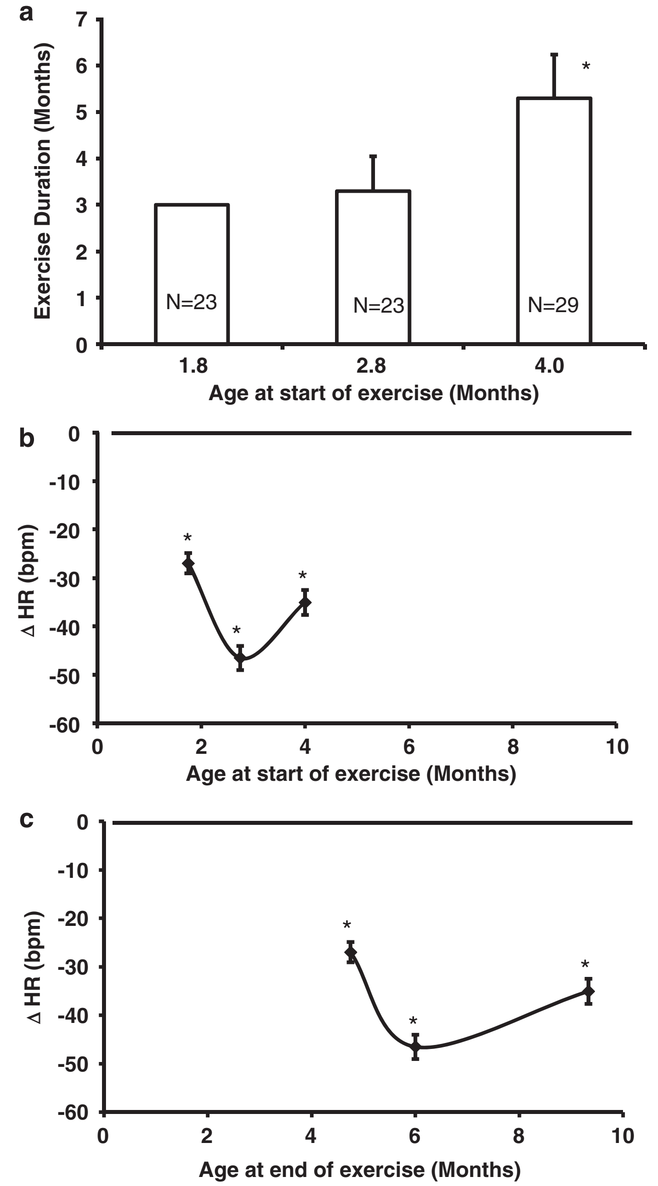

Figure 3 Effect of the age of animals on exercise-dependent changes in heart rates. Animals were grouped according to their age at the beginning of the exercise training. (**a**) Bars represent the number of rats per group and indicate the mean exercise duration of these groups. (**b**) Difference in heart rates between rats performing exercise and their sedentary controls for the three groups defined above. (**c**) Differences in heart rate between rats performing exercise and their sedentary controls for groups defined by similar age at the end of exercise. Data are means ± s.e.; **P*<0.05 *vs.* sedentary controls.

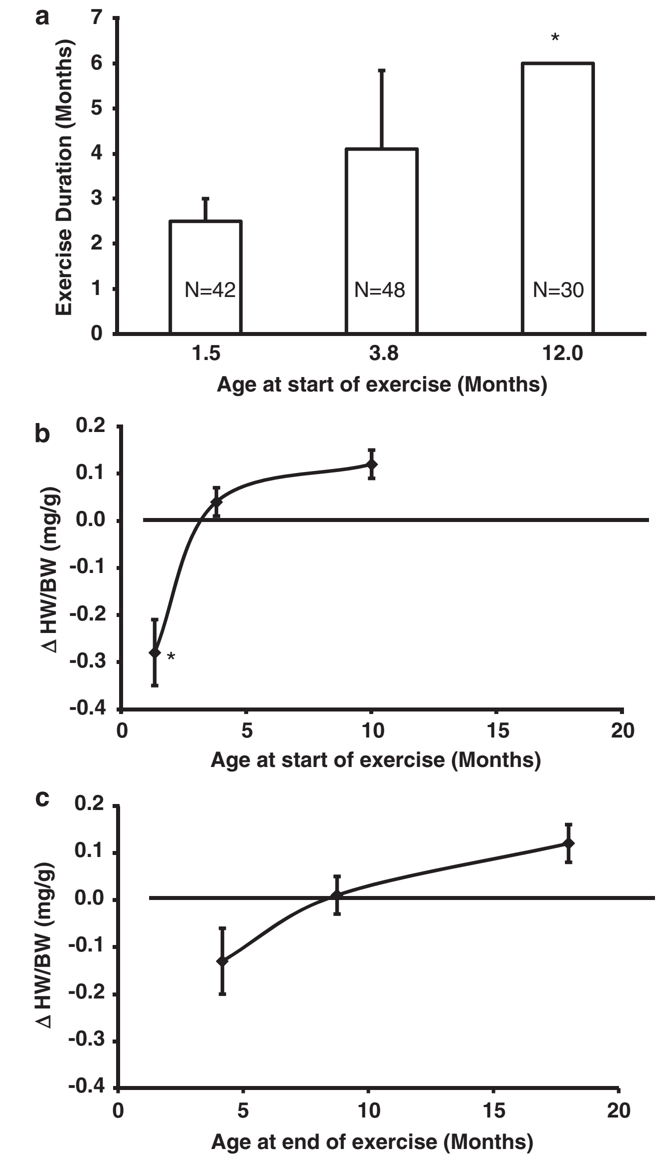

Figure 4 Effect of the age of animals on exercise-dependent changes in heart weight-to-body weight ratio (HW/BW). (**a**) Bars represent number of rats per group and indicate the mean exercise duration of these groups. (**b**) Difference in HW/BW between rats performing exercise and their sedentary controls for the three groups defined above. (**c**) Difference in HW/BW between rats performing exercise and their sedentary controls for groups defined by similar age at the end of exercise. Data are given as the difference between non-trained (sedentary) and trained SHR in mg g^{-1}. Data are means ± s.e.; **P*<0.05 *vs.* sedentary controls.

using young SHR at the age of 1.0–1.5 months and an exercise duration of 2–3 months were used to compare the effect of treadmill *vs.* free running wheel exercise protocols.[14–16,22] Systolic blood pressures were quite similar in these studies. Furthermore, a similar difference in blood pressure was observed in both groups, as expected for these young rats (Figure 6a). The effect of exercise on heart weight-to-body weight ratio was determined in two of these studies.[15,22] Although authors report a 15% increase in heart weight-to-body weight ratio in the free running group in the presence of a 6% decrease in blood pressure, they report about a 9% reduction in heart weight-to-body weight ratio in the treadmill group in the presence of a 5% decrease in blood pressure (Figure 6b). The data indicate that the form of training differentially modulates hypertrophy, irrespective of blood pressure.

Sex-specific difference in studies on effects of exercise

The data analysis presented above did not distinguish between male and female SHR. When considering the sex-specific differences, it is obvious that female rats were preferentially used in studies with older rats. As a consequence, female rats had longer exercise duration and weaker effects on blood pressure (Table 2). Therefore, sex-specific

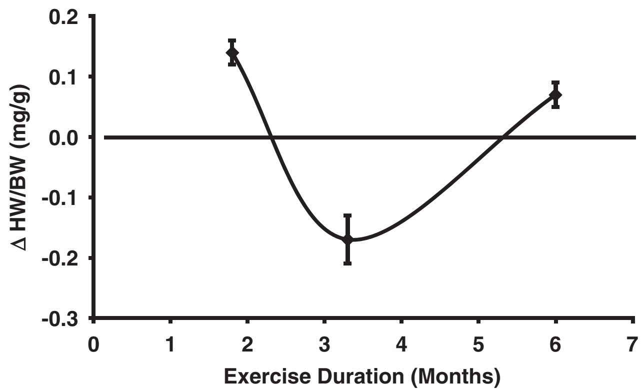

Figure 5 Effect of the duration of exercise on changes in heart weight-to-body weight ratio (HW/BW). Data are given as the difference between non-trained (sedentary) and trained SHR in $mg\,g^{-1}$. Data are means ± s.e.

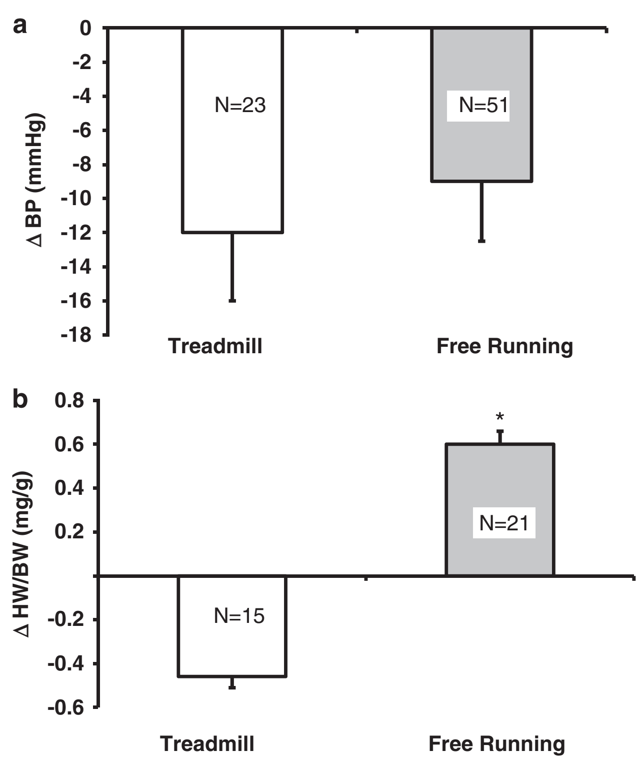

Figure 6 Effect of the type of exercise on blood pressure and heart weight-to-body weight ratio (HW/BW). Data are given for studies using rats at the age of 1.0–1.5 months, subjected to exercise protocols for 2–3 months. (**a**) Changes in blood pressure. (**b**) Changes in HW/BW. Data are given as the difference from sedentary controls. Data are means ± s.e.; *$P<0.05$ *vs.* treadmill.

differences can only be analyzed when comparing studies that use rats at the same age and with similar training intensity. Three studies used 2-month-old SHR with a 3-month treadmill protocol, but either male or female rats in order to compare the effects of sex.[25–27] Under these conditions, the difference in systolic blood pressure at the end of the exercise protocol was −7 mm Hg in the female group (n=12) and −14 mm Hg in the male group (n=14). This suggests that the observed effects of age and exercise duration on blood pressure are at least in part independent of sex. When considering the influence of sex on heart rate reductions, no significant differences were observed between female and male rats (Table 3). No comparison can be performed with regard to the effect of sex on heart weight-to-body weight ratio, because such studies are not available.

Table 2 Influence of sex on exercise-induced changes in BP

	Male	*Female*
N (sed/ex)	111/114	71/71
Age (months)	1.6 ± 0.6	3.5 ± 0.8, $P<0.05$
Exercise duration (months)	2.8 ± 0.8	4.1 ± 1.2, NS
BP (syst) sed (mm Hg)	207.6 ± 26.2	182.6 ± 5.6, $P<0.05$
BP (syst) ex (mm Hg)	194.0 ± 33.9	181.7 ± 7.4, NS
Δ BP (syst) (mm Hg)	−13.6	−0.9

Abbreviations: BP, blood pressure; ex, exercise-performing rats; NS, not significantly different; sed, sedentary rats; syst, systolic BP.

Table 3 Influence of sex on exercise-induced changes in blood pressure and heart rate when age-matched rats were considered

	Male	*Female*
N (sed/ex)	35/35	40/39
Age (months)	2.2 ± 0.6	3.6 ± 0.6, NS
Exercise duration (months)	2.8 ± 0.2	5.0 ± 1.0, $P<0.05$
HR sed (b.p.m.)	389 ± 31	481 ± 35, $P<0.05$
HR ex (b.p.m.)	350 ± 16	448 ± 38, $P<0.05$
Δ HR (b.p.m.)	−39	−33

Abbreviations: ex, exercise-performing rats; HR, heart rate; NS, not significant; sed, sedentary rats.

DISCUSSION

In this study, we investigated the effect of age and duration of exercise on blood pressure, heart rate and heart weight-to-body weight ratio in a large population of rats by performing a meta-analysis of 18 studies using the same genetic model of hypertension (SHR). It is noteworthy that the studies used different inbred strains, different sexes and different exercise protocols. So that the use of different methods to quantify the blood pressure did not present a confounding variable, this study is based exclusively on investigations using the tail-cuff method. Independent of these limitations, the published data allowed us to perform such an analysis on the basis of a large number of animals and to investigate the effects of age and duration of exercise, which were not addressed in any previous study. The main result of this study is that neither prolonged exercise nor exercise in rats with established hypertension reduces blood pressure or induces a favorable antihypertrophic effect. Moreover, depending on the type of exercise, the incidence of myocardial hypertrophy may be increased in rats with established hypertension. In contrast, exercise seems to reduce resting heart rate, irrespective of all other variables.

Exercise and physical activity are currently recommended for patients with high-normal blood pressure and hypertension without additional major risk factors.[2–4] These are recommendations that include other lifestyle modifications, such as cessation of smoking and lowering fat and salt intake. It is therefore difficult to determine whether there is a specific effect of exercise on blood pressure. A recent meta-analysis of randomized controlled trials reported a small but significant effect on blood pressure reduction at low or moderate intensity with no further effect at higher intensities, based on 29 studies with 1533 hypertensive and normotensive participants.[33]

There was nevertheless great heterogeneity among the different trials, and no information was given with regard to the age and weight of participants. Moreover, studies in patients normally lack adequate control groups.[34] It is therefore difficult to predict from clinical trials the advantage or risk of exercise in hypertensive individuals. To address this question, experimental studies that are based on a large number of animals and possess high reproducibility in different laboratories are required. Both requirements can be met with a meta-analysis, as we have performed here. Following this approach, blood pressure-lowering effects caused by physical activity cannot be predicted in individuals with established hypertension. On the other hand, exercise may prevent the onset of hypertension in subjects with a genetic predisposition to hypertension. Of note, blood pressure-lowering effects were obtained in pre-hypertensive SHR or in early hypertension.

Our conclusion is based on the collection of data published by different laboratories with similar but not identical methods. It should be noted that some limitations are still evident. As sex-specific differences cannot be ruled out completely, it should be kept in mind that nearly all studies using young SHR used males, whereas studies using SHR at an advanced age preferentially used females. This is due to the higher level of spontaneous running activity in female rats.[32] A sex-dependent effect has been suggested before.[18] However, no obvious difference was noted between males and females in the individual groups in terms of blood pressure reduction when compared on the basis of the same age and the same duration of exercise. In addition, the blood pressure difference between training and sedentary groups at the end of the study was +1 mm Hg in 16-month-old females and +4 mm Hg in 15-month-old males.[7,12] Therefore, we do not expect that sex-dependent differences are more important than the age at the start of the exercise protocol, although the latter data are given only for spontaneously hypertensive heart failures.

Furthermore, it is not clear whether treadmill protocols are more appropriate than free access to running wheels when blood pressure is used as a parameter. On one hand, rats on treadmill protocols often adjusted to their individual exercise capacity and trained thereafter at approximately 50% of maximal capacity. This resulted in significantly smaller running distances per week compared with rats with free access to running wheels. Furthermore, rats on treadmills had periodic running-free days. On the other hand, rats on treadmills performed one running bout for 45–75 min a day, whereas rats with free access to running wheels averaged 167 running bouts for 43 s each.[35] Therefore, the treadmill approach does not constitute a physiological type of running behavior. The same trends observed overall for the entire group of rats were observed when comparing rats that ran on running wheels to those that ran on treadmills. For example, 1-month-old rats on treadmills exhibited a 17 mm Hg reduction in blood pressure, but rats aged 6 months exhibited a reduction of only 7 mm Hg.[21,14] The only remarkable observation is that older rats on treadmills did not tolerate this well, although they are reported to achieve longer running distances on running wheels. The lower treadmill tolerance obviously indicates a limitation in age-dependent stress tolerance rather than exercise capacity.

Despite the lack of effect on resting blood pressure in these animals, there was also a clear trend toward a further increase in myocardial hypertrophy that exceeded that of non-trained SHR. Again, a favorable effect cannot be predicted from these findings based on exercise alone. In general, exercise has been reported to reverse adverse hypertrophy.[11,36,37] However, a clear molecular characterization of this type of hypertrophy or exercise-reversed hypertrophy in the absence of hypertension has not yet been performed. This topic requires specific attention, as hypertrophic cardiomyopathy is the major cardiovascular cause of sudden cardiac death in young competitive athletes.[38] Furthermore, the data published suggest that the type of exercise (running wheels *vs.* treadmills) affects the incidence of myocardial hypertrophy.

It is noteworthy that only a few studies that have been published on this topic combine exercise with the administration of a standard blood pressure-lowering medication, such as an angiotensin converting enzyme inhibitor. Angiotensin converting enzyme inhibitors have been shown to lower blood pressure, limit end-organ damage and increase survival in this model.[28] Indeed, the interaction between angiotensin converting enzyme inhibition and exercise requires more attention as it mimics the situation normally occurring in hypertensive patients, specifically in patients that display blood pressures as high as those seen in SHR at an advanced stage.

Finally, the data not only indicate that there is no beneficial effect of exercise on established high blood pressure, but also identify a potential risk of endurance exercise on the background of hypertension without efforts to control blood pressure. This might have specific implications for non-professional runners who commonly participate in city marathons.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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