Regular physical exercise reduces blood pressure and is broadly recommended by current American and European hypertension guidelines.1,2 Hypertensives are encouraged to “engage in aerobic exercise on a regular basis, such as walking, jogging or swimming for 30 to 45 minutes daily.”2 In normotensives, regular exercise reduces systolic blood pressure by 3 to 5 mm Hg and diastolic blood pressure by 2 to 3 mm Hg. In hypertensives, this effect is even more pronounced: a recent meta-analysis indicated a mean reduction of 7 mm Hg systolic and 5 mm Hg diastolic.3 To date, however, there are no trials on the effect of exercise on resistant hypertension. Resistant hypertension is a common problem faced by both primary care clinicians and specialists. Its exact prevalence is unknown, but it is estimated to range from 10% to 30% of all hypertensive patients.4 Resistant hypertension is defined as the failure to achieve blood pressure target by ≥3 antihypertensive agents, 1 of which is a diuretic.5 Thus, this entity is defined by its resistance to drug therapy. It remains elusive, however, whether a reduced responsiveness to drug therapy goes along with a reduced responsiveness to alternative approaches to lower blood pressure as well. The present work is a parallel group randomized controlled trial investigating the hypothesis that an aerobic exercise program is able to reduce blood pressure in resistant hypertension.

Methods

Study Population
Patients were recruited from our hypertension outpatient clinic and by press announcement. In accordance with the 2008 American Heart Association scientific statement, resistant hypertension was defined as a blood pressure ≥140/90 mm Hg in spite of concurrent use of 3 antihypertensive agents of different classes in adequate doses or a blood pressure that is controlled with ≥4 antihypertensive agents (inclusion criteria).5 Exclusion criteria were regular engagement in physical exercise training in the past 4 weeks before inclusion in the study, symptomatic peripheral arterial occlusive disease, aortic insufficiency or stenosis more than stage I, hypertrophic obstructive cardiomyopathy, congestive heart failure (more than New York Heart Association II), uncontrolled cardiac arrhythmia with hemodynamic relevance, systolic office BP ≥180 mm Hg, signs of acute ischemia in exercise ECG, and change of antihypertensive medication in the past 4 weeks before inclusion in the study or during follow-up period. According to these criteria, 50 patients (29 women and 21 men) were enrolled and randomized to exercise and control group by lot (Figure 1). Patient characteristics including concomitant diseases are presented in Table 1. The median number of antihypertensive drugs for each patient was ranging from 3 to 7. We included 14 individuals with 3 antihypertensive drugs and uncontrolled hypertension and 36 subjects with ≥4 antihypertensive drugs. Antihypertensive medication contained diuretics, calcium-channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II type 1 blockers, aliskiren, α-blockers, moxonidine, clonidine, and minoxidil. The preexisting antihypertensive medication remained unchanged throughout the study. To minimize the bias...
of compliance concerning antihypertensive drug intake during the study, all of the patients in the exercise and control groups were insistently and repeatedly requested to take care of an accurate drug intake. Written informed consent was obtained from all of the participants before inclusion in the study. The study was approved by the local ethics committee at the Charité Berlin.

**Protocol**

Assessment of 24-hour ambulatory blood pressure (ABP) monitoring, physical performance, vascular compliance, and cardiac index were performed before and after the observation period. The impact of daytime ABP has been shown to be of higher relevance for cardiovascular risk than nighttime ABP. Therefore, a significant decrease in daytime systolic ABP was defined as a primary end point. Assessment of physical performance was carried out by a treadmill stress test using a modified Bruce protocol (begin with 3 km/h, increase of speed by 1.4 km/h after 3 minutes, thereafter increase of elevation by 3% at constant speed) under continuous ECG monitoring and assessment of oxygen uptake and CO2 release.

In this protocol each workload corresponds with an increase of 25 W for a patient of 75 kg weight. Assessment of maximal oxygen uptake is the gold standard for the determination of physical performance. Validity of results, however, depends on subjects exercising until exhaustion. In the elderly, the duration of the exercise test is often limited by muscular or articular discomfort rather than by exhaustion. Hence, we decided to determine changes in physical performance not only by maximal oxygen uptake but also by assessment of lactate curves. This method does not depend on compliance and allows a reliable and valid estimation of physical performance.

Lactate concentration in capillary blood was determined at the end of each workload (Ebioplus, Eppendorf, Hamburg, Germany). The level of perceived exertion was assessed by the 15-point Borg scale ranging from 6 to 20, with “6” corresponding with a “very, very light effort” and “20” corresponding with “exhaustion.” Comparison of lactate concentrations, rate of perceived exertion, and blood pressure on exertion was performed using the data of the individual workloads reached at both baseline and follow-up examination. Twenty-four-hour ABP monitoring was performed using SpaceLabs 90207 monitors (SpaceLabs, Redmond, WA). Intervals between single measurements were set to be 20 minutes during daytime (6:00 AM to 10:00 PM) and 30 minutes during nighttime (10:00 PM to 6:00 AM). Assessment of small and large artery compliance was performed using pulse wave analysis by means of the CR-2000 instrument (Hypertension Diagnostics, Eagan, MN), as published previously.

Arterial compliance and office blood pressure were calculated as the mean of 3 measurements. The follow-up blood pressure and vascular measurements of the training group were conducted within 5 days after the last training session.

The training program, consisting of walking on a treadmill according to an interval-training pattern, was carried out 3 times weekly for 8 to 12 weeks with a target lactate concentration of 2.0±0.5 mmol/L in capillary blood slightly above the aerobic threshold, as described previously. Subjects were asked to participate for 12 weeks and (if not able to schedule the 3 times weekly training sessions for the whole period) a minimum of 8 weeks.

**Sample Size Estimation**

Based on previous studies on exercise in hypertension, we expected the intervention to result in a decrease of daytime systolic 24-hour ABP (primary end point) of ≥6 mm Hg in the training group with no changes in the control group. This difference was considered to be clinically relevant. A sample size of 23 in each group has 80% power to detect this difference assuming that the common SD is 7 mm Hg with a 2-sided *P* <0.05. We estimated the dropout rate to be 5% to 10%, leading to an overall sample size of 50 patients.

**Statistical Analysis**

Numeric data are presented as mean±SD and number of antihypertensive drugs as median and range. Data were tested for normal
these cases, the results of baseline stress tests were excluded from analysis. The follow-up examination, all of the patients of both exercise and control groups stated that there was no change of compliance in the course of the study. Table 2 presents ABP data, office blood pressure, vascular compliance, and cardiac index in training and control groups before and after the observation period. An ANCOVA model adjusted for baseline values, age, and diabetes mellitus was used to analyze the impact of the exercise training on the cardiovascular system. The exercise program significantly reduced daytime systolic and diastolic ABPs by 5.9 ± 11.6 and 3.3 ± 6.5 mm Hg, respectively (P = 0.03 each; Table 2). Nighttime systolic and diastolic ABPs were numerically lower after the exercise program, but changes did not reach significance (−3.8 ± 17.1 and −1.9 ± 8.2 mm Hg; P > 0.05 each; Table 2). Twenty-four-hour systolic and diastolic ABPs were significantly decreased by 5.4 ± 12.2 (P = 0.03) and 2.8 ± 5.9 mm Hg (P = 0.01). Systolic and diastolic office blood pressures were numerically but not significantly reduced by the exercise training (−6.6 ± 15.7 and −2.7 ± 8.0 mm Hg; P value not significant), with changes < 1 mm Hg in the control group. Pulse wave analysis revealed no alterations of large and small artery elasticity in the exercise and control groups in the course of the observation period (P value not significant for each; Table 2). Cardiac index at rest remained unchanged by the exercise program (P value not significant).

The exercise program led to an increase in physical performance, as illustrated by an increase of maximal oxygen uptake from 22.8 ± 5.7 to 24.3 ± 5.1 mL/kg⋅min (P < 0.01; Table 2) and by a right shift of lactate curves (Figure 2). The exercise program allowed a significant increase in mean maximal workload level of the Bruce protocol from 5.7 ± 1.7 to 6.6 ± 1.4 (P < 0.01) with no change in the control group (4.3 ± 1.6 to 4.0 ± 1.6). Perceived exertion as measured by the Borg scale decreased in the exercise group without significant
distribution by the Kolmogorov-Smirnov test. Intergroup differences at baseline were tested by unpaired 2-tailed t tests for numeric parameters. Comparison of categorical parameters was performed by Fisher exact test in case of dichotomy and by Pearson χ² test in case of polychotomy. Changes of numeric parameters from baseline to follow-up were analyzed using an ANCOVA model. Because the exercise-induced reduction of blood pressure depends on baseline values, age, and diabetes mellitus, we included these parameters as covariates in the ANCOVA model. P < 0.05 was regarded significant. Treadmill stress test findings were analyzed by using data of covariates in the ANCOVA model.

### Results

Baseline data of exercise and control group are presented in Table 1. Kolmogorov-Smirnov tests showed a Gaussian distribution of systolic and diastolic daytime, nighttime, and 24-hour ABP in both exercise and control groups. One subject in the exercise group discontinued the exercise program because of need for abdominal surgery independent of the study. One patient in both the exercise and the control groups reported a change in antihypertensive medication at the follow-up examination, and data were excluded from analysis. Thus, there were 2 dropouts in the exercise group and 1 in the control group. The mean follow-up period was 9.8 ± 2.0 weeks in the exercise group and 10.2 ± 2.0 weeks in the control group (P value not significant). The exercise program was well tolerated by all of the patients. Mean training lactate concentration was 1.6 ± 0.6 mmol/L, corresponding with a mean training heart rate of 100.3 ± 11.6 per minute. Four patients did not redo the treadmill stress test. In these cases, the results of baseline stress tests were excluded

### Table 2. Twenty-Four-Hour ABP, Office BP, Arterial Compliance, Maximal Oxygen Uptake, Cardiac Index, Weight, and Body Mass Index in Exercise and Control Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Exercise (n=24; 2 Dropouts)</th>
<th>Control (n=26; 1 Dropout)</th>
<th>Δ</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime systolic ABP, mm Hg</td>
<td>138.4 ± 14.1</td>
<td>132.5 ± 10.8</td>
<td>−5.9 ± 11.6</td>
<td>131.2 ± 13.0</td>
</tr>
<tr>
<td>Daytime diastolic ABP, mm Hg</td>
<td>78.3 ± 10.2</td>
<td>75.0 ± 9.8</td>
<td>−3.3 ± 6.5</td>
<td>72.3 ± 9.1</td>
</tr>
<tr>
<td>Nighttime systolic ABP, mm Hg</td>
<td>129.8 ± 18.5</td>
<td>126.0 ± 10.2</td>
<td>−3.8 ± 17.1</td>
<td>123.3 ± 13.3</td>
</tr>
<tr>
<td>Nighttime diastolic ABP, mm Hg</td>
<td>70.5 ± 10.0</td>
<td>68.6 ± 10.3</td>
<td>−1.9 ± 8.2</td>
<td>66.0 ± 9.5</td>
</tr>
<tr>
<td>24-h systolic ABP, mm Hg</td>
<td>135.3 ± 15.2</td>
<td>129.9 ± 10.0</td>
<td>−5.4 ± 12.2</td>
<td>128.7 ± 12.2</td>
</tr>
<tr>
<td>24-h diastolic ABP, mm Hg</td>
<td>75.4 ± 9.5</td>
<td>72.6 ± 9.7</td>
<td>−2.8 ± 5.9</td>
<td>70.2 ± 9.1</td>
</tr>
<tr>
<td>Systolic office BP, mm Hg</td>
<td>141.8 ± 16.3</td>
<td>135.0 ± 13.2</td>
<td>−6.6 ± 15.7</td>
<td>140.2 ± 19.5</td>
</tr>
<tr>
<td>Diastolic office BP, mm Hg</td>
<td>78.1 ± 9.1</td>
<td>75.3 ± 8.0</td>
<td>−2.7 ± 8.0</td>
<td>74.6 ± 10.7</td>
</tr>
<tr>
<td>Large artery compliance, mL/mm Hg×10</td>
<td>12.0 ± 4.5</td>
<td>11.8 ± 3.7</td>
<td>−0.2 ± 5.7</td>
<td>12.9 ± 4.6</td>
</tr>
<tr>
<td>Small artery compliance, mL/mm Hg×100</td>
<td>5.7 ± 3.1</td>
<td>5.1 ± 3.7</td>
<td>−0.5 ± 2.5</td>
<td>4.9 ± 2.6</td>
</tr>
<tr>
<td>Maximal oxygen uptake, mL/kg×min</td>
<td>22.8 ± 5.7</td>
<td>24.3 ± 5.1</td>
<td>1.4 ± 3.7</td>
<td>21.5 ± 4.9</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.5 ± 0.3</td>
<td>2.4 ± 0.5</td>
<td>−0.1 ± 0.6</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>85.7 ± 17.1</td>
<td>85.4 ± 17.8</td>
<td>−0.2 ± 1.7</td>
<td>84.0 ± 14.1</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.9 ± 4.4</td>
<td>28.8 ± 4.6</td>
<td>0.1 ± 0.6</td>
<td>29.9 ± 4.7</td>
</tr>
</tbody>
</table>

ABP indicates ambulatory blood pressure; BP, blood pressure; Δ, change of parameter in observation period. Data are presented as mean ± SD. Intergroup differences in the changes of parameters from baseline to follow-up were analyzed using an ANCOVA model adjusted for age, baseline value, and diabetes mellitus. *P < 0.05 was regarded significant.
changes in the control group (Figure 2). The exercise program significantly lowered both systolic and diastolic blood pressures on exertion (Figure 2). A correlation analysis of the difference of systolic daytime ABP in the exercise group with the mean reduction of lactate during treadmill stress tests revealed a Pearson coefficient of 0.08 ($P<0.97$), indicating that there was no significant correlation of the extent of improvement of physical performance and the reduction of systolic daytime ABP. Accordingly, there was no significant correlation between decrease of systolic daytime ABP and change of maximal oxygen uptake (Pearson coefficient, $-0.19; P=0.44$).

Discussion

The present data show that aerobic exercise leads to a significant reduction of blood pressure in resistant hypertension. Hence, a low responsiveness to antihypertensive drug therapy does not inevitably go along with a low responsiveness to exercise. The extent of exercise-induced reduction of blood pressure varies considerably from study to study, ranging from 5 to 15 mm Hg. A recent meta-analysis found a mean reduction of $-7/5$ mm Hg. In older hypertensives (like the present study population), the effect is not as pronounced as in younger individuals and has been shown to be 5 to 6 mm Hg. Thus, the present study's systolic blood pressure reduction of 6 mm Hg in resistant hypertension is not lower than the anticipated range in nonresistant hypertension. This fact is remarkable for 3 reasons. First, exercise was successful in reducing blood pressure in a situation of low responsiveness to drug treatment. Second, the decrease was assessed in ABP and not in office blood pressure. The risk of hypertensive cardiovascular complications correlates more closely with ABP than with office pressure. Third, the mean baseline systolic blood pressure of 138 mm Hg was in the high-normal rather than the hypertensive range. Because the exercise-induced reduction of blood pressure increases with baseline blood pressure, an even more pronounced effect may be expected with higher initial blood pressure. A decrease of 6 mm Hg in systolic and 3 mm Hg in diastolic ABP is of clinical relevance with regard to cardiovascular risk; for example, a blood pressure reduction of 5/2 mm Hg has been demonstrated to reduce the first incidence of fatal and nonfatal stroke by 29%. Interestingly, the present beneficial effects of exercise on blood pressure are more pronounced at daytime than at nighttime. This finding has been described before. On the one hand, the effects may be less impressive
because of the lower baseline blood pressure at night. On the other hand, it is well known that regular exercise reduces sympathetic tone, and sympathetic tone is lower at nighttime than at daytime.\textsuperscript{3} Data were adjusted for baseline values, because the exercise-induced reduction in blood pressure is more pronounced in high baseline blood pressures.\textsuperscript{12} Furthermore, data were adjusted for age and diabetes mellitus, because the cardiovascular impact of sports may be attenuated in older and diabetic patients.\textsuperscript{19} The exercise-induced numeric reduction of systolic office blood pressure is comparable to the changes in ABP (\textminus7 versus \textminus6 mm Hg). These changes show higher SDs and do not reach significance in the ANCOVA model. Office blood pressure can be influenced by white coat effect and other situational stress factors related to the study setting, which may explain the higher SD. The study size calculation, however, was based on the lower SD of ABP.

There is a multitude of reasons for resistant hypertension, including nonadherence, secondary hypertension, increased vascular stiffness, obesity, increased sympathetic tone, and high sodium load.\textsuperscript{4} Increased vascular stiffness can be an important cause of resistant hypertension.\textsuperscript{20} Accordingly, our study population revealed a reduced compliance of capacitance and oscillatory arteries, as indicated by the $C_1$ and $C_2$ values in Table 2. Arterial stiffness goes along with a loss of sensitivity toward antihypertensive therapy, because the majority of antihypertensive drugs are vasodilators. The vasodilatory potency of a drug is higher in elastic arteries than in stiff arteries with advanced atherosclerotic wall changes. So how can it be explained that exercise is nevertheless able to reduce blood pressure? Regular exercise positively affects $\geq$3 of the above-mentioned reasons for resistant hypertension, obesity, increased sympathetic tone, and high sodium load.\textsuperscript{3} Moreover, sports augment endothelium-dependent vasodilation by increased production of NO.\textsuperscript{21} We have shown previously that this improvement of endothelial function is independent of pulse pressure as a marker of vascular aging.\textsuperscript{12} Vascular stiffness did not impede the blood pressure–lowering effects of exercise.\textsuperscript{22} Body weight remained constant from baseline to control, thus excluding a reduction of blood pressure by weight loss. We cannot provide data on further markers of body composition like waist circumference, which has to be regarded as a limitation of the study.

The exercise program led to an improvement of physical performance, as indicated by the increase in maximal oxygen uptake and the right shift of the lactate curves (Table 2 and Figure 2). The level of perceived exertion was lower at the follow-up treadmill stress test as well. This is of interest not only with regard to quality of life. A recent study including $>6000$ men revealed that exercise capacity is a more powerful predictor of mortality than other established risk factors for cardiovascular disease.\textsuperscript{22} With regard to elevations of blood pressure on exertion, it is important to keep in mind that the recommended training intensity is “moderate.”\textsuperscript{11,12} Lowering blood pressure in hypertension does not necessitate a higher training intensity.\textsuperscript{3,15} In daily life, the performance of exercise in hypertension is usually not monitored by a sophisticated method like lactate concentration. Therefore, the recommendation of training intensity has to be kept more practical. In the present lactate-directed exercise program, as a rule of thumb, the patients were never too exhausted to be able to conduct a conversation during a training session. Mean training heart rate was $\approx$100 per minute. It has to be taken into account, however, that 68% of the subjects in the exercise group were on $\beta$-blockers. This kind of training was well tolerated and induced a measurable cardiovascular benefit. Moreover, the beneficial cardiovascular effects of regular exercise are not limited to a reduction of blood pressure. Regular aerobic exercise counteracts other important cardiovascular risk factors as well: it leads to a reduction of weight in obese patients, it decreases low-density lipoprotein cholesterol while increasing high-density lipoprotein cholesterol, it augments insulin sensitivity, and it reduces endothelial dysfunction.\textsuperscript{23}

A low responsiveness of hypertension to drug therapy may intuitively evoke the impression that if this multitude of antihypertensive drugs is not able to provide blood pressure control, lifestyle modifications won’t do anyway. In a recent trial on resistant hypertension, salt restriction lowered systolic and diastolic blood pressures by 22.7 and 9.1 mm Hg, respectively.\textsuperscript{24} Our data show that regular exercise is able to lower blood pressure in resistant hypertension as well. Even if we have to prompt patients to maximal therapeutic options like renal sympathetic denervation or baroreceptor stimulation, these approaches should always be accompanied by recurrent recommendations of lifestyle modifications like regular exercise.

**Perspectives**

Patients with resistant hypertension are at high risk for adverse cardiovascular events. There are few data on the effects of lifestyle modification in resistant hypertension. The present study shows that a low responsiveness to pharmacological therapy does not mandatorily mean a low responsive-ness to nonpharmacological approaches. Aerobic exercise on a regular basis is a helpful adjunct to control blood pressure and should be included in the therapeutic approach to resistant hypertension.

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**Disclosures**

None.

**References**


Novelty and Significance

What Is New?

- Aerobic exercise on a regular basis reduces blood pressure in resistant hypertension.
- Aerobic exercise improves physical performance in resistant hypertension.
- A training of moderate intensity is well tolerated by resistant hypertensives.

What Is Relevant?

- A low responsiveness to pharmacological therapy does not mandatorily mean a low responsiveness to exercise.

Exercise should be included in the therapeutic approach to resistant hypertension.

Summary

The present work is the first trial on the effects of physical exercise in resistant hypertension. It shows that exercise is a helpful adjunct to control blood pressure in this setting.
Aerobic Exercise Reduces Blood Pressure in Resistant Hypertension
Fernando Dimeo, Nikolaos Pagonas, Felix Seibert, Robert Arndt, Walter Zidek and Timm H. Westhoff

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