Aerobic Exercise Training Does Not Modify Large-Artery Compliance in Isolated Systolic Hypertension

Kathryn E. Ferrier, Tamara K. Waddell, Christoph D. Gatzka, James D. Cameron, Anthony M. Dart, Bronwyn A. Kingwell

Abstract—The present study characterized large-artery properties in patients with isolated systolic hypertension (ISH) and determined the efficacy of exercise training in modifying these properties. Twenty patients (10 male and 10 female) with stage I ISH and 20 age- and gender-matched control subjects were recruited, and large-artery properties were assessed noninvasively. Ten ISH patients (5 male and 5 female) were enrolled in a randomized crossover study comparing 8 weeks of moderate intensity cycling with 8 weeks of sedentary activity. Brachial and carotid systolic, diastolic, mean, and pulse pressures were higher in the ISH group than in the control group. Systemic arterial compliance (0.43±0.04 versus 0.29±0.02 arbitrary compliance units for the control versus ISH groups, respectively; \( P=0.01 \)) was lower, and carotid-to-femoral pulse-wave velocity (9.67±0.36 versus 11.43±0.51 m·s\(^{-1}\) for the control versus ISH groups, respectively; \( P=0.007 \)), input impedance (2.39±0.19 versus 3.27±0.34 mm Hg·s·cm\(^{-1}\) for the control versus ISH groups, respectively; \( P=0.04 \)), and characteristic impedance (1.67±0.17 versus 2.34±0.27 mm Hg·s·cm\(^{-1}\) for the control versus ISH groups, respectively; \( P=0.05 \)) were higher in the ISH group than in the control group. Training increased maximal oxygen consumption by 13±5\% (\( P=0.04 \)) and maximum workload by 8±4\% (\( P=0.05 \)); however, there was no effect on arterial mechanical properties, blood lipids, or left ventricular mass or function. These results suggest that the large-artery stiffening associated with ISH is resistant to modification through short-term aerobic training. (Hypertension. 2001;38:222-226.)

Key Words: hypertension, isolated systolic arteries compliance exercise aorta

Isolated systolic hypertension (ISH) contributes to cardiovascular morbidity and is an important predictor of death from coronary heart disease and stroke.\(^{1,2}\) The proportion of hypertensive patients with ISH has doubled over the past 20 years,\(^{3}\) with \( \approx 26\% \) of the total population age \( \geq 55 \) years affected.\(^{4}\) Thus, ISH is the most common form of hypertension in the rapidly expanding older population. Stiffening of the large proximal arteries is recognized as the cause of ISH\(^{5,6}\) and occurs as a result of age-related deterioration in elastic fibers and also the atherosclerotic process.\(^{7}\) The consequent increase in systolic blood pressure (SBP) contributes to increased cardiac afterload and left ventricular hypertrophy,\(^{8}\) whereas reduced diastolic blood pressure (DBP) may impair subendocardial perfusion, particularly in the setting of coronary artery disease.\(^{9,10}\)

Hypertension treatment guidelines now reflect the important role of SBP with regard to cardiovascular risk, and the benefits of pharmacological treatment have recently been convincingly demonstrated with the conclusion of 3 large trials: Systolic Hypertension in the Elderly Program (SHEP),\(^{11}\) Systolic Hypertension in Europe (Syst-Eur),\(^{12}\) and Systolic Hypertension in China (Syst-China).\(^{13}\) Although different antihypertensive drugs were used, similar results were reported in all trials, with reduction in total stroke incidence of 36% to 42% compared with placebo. All fatal and nonfatal cardiovascular end points were also reduced with active treatment by 26% to 37%.

Although the beneficial effects of lowering SBP on cardiovascular events in ISH have been proven, the effectiveness of antihypertensive drug therapy may be limited by the detrimental effects of further reductions in diastolic pressure,\(^{14}\) which could potentially contribute to myocardial ischemia.\(^{9}\) Exercise training is a promising alternate therapy with proven efficacy in both normotensive subjects and those with essential hypertension.\(^{15-18}\) Endurance-trained athletes have higher large-artery compliance than do their sedentary counterparts,\(^{19-22}\) and moderate aerobic exercise increases large-artery compliance after 4 weeks in young normotensive but previously sedentary subjects.\(^{23}\) The present study sought to examine the efficacy of a similar training regimen to increase large-artery compliance and reduce SBP in a young elderly population with stage I ISH. Large-artery properties in ISH patients were compared with a matched normotensive control group. Ten individuals from the patient group were then enrolled in a randomized crossover design study incorporating both 8 weeks of home-based cycle training per-
formed 3 times per week at 65% of maximum capacity and 8 weeks of normal sedentary activity.

Methods
All participants gave informed consent for participation in the study, which was undertaken with the approval of The Alfred Healthcare Group Ethics Committee and performed in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Subjects and Study Design
Twenty patients with stage I ISH (10 males and 10 females age 64±7 [mean±SD] years) and 20 age- and gender-matched control subjects (age 64±7 years) were recruited. Inclusion criteria for stage I ISH were a casual clinic SBP >150 mm Hg and DBP <90 mm Hg. Normal subjects had casual SBP <140 mm Hg and DBP <90 mm Hg. The exclusion criteria were age >75 years, antihypertensive medication, excess alcohol consumption (>4 standard drinks per day), coronary artery disease (based on history, examination, and exercise stress testing), other major medical illness, involvement in a regular exercise program, and smoking. None of the female participants were taking hormone replacement therapy. Ten of the ISH patients (5 males and 5 females age 64±7 years) were enrolled in a randomized crossover design study comparing 8 weeks of moderate exercise with 8 weeks of normal sedentary activity.

Study Protocol
During a single visit, all subjects had measurements of supine blood pressure, arterial compliance, central and peripheral pulse-wave velocity (PWV), aortic input impedance, and lipid profile. Patients enrolled in the exercise intervention had a number of additional measurements, including maximal oxygen consumption (VO2 max) and left ventricular structure and function measured at baseline, and all measurements were repeated at the completion of both the exercise and sedentary interventions. All measurements were made at least 48 hours after the last bout of exercise.

Exercise Training
A Repco Compucycle No. RC500 exercise bicycle (AS-4092) was provided for each subject during the exercise phase of the study; the subjects rode the bicycle 3 times per week at an intensity of 65% of their predetermined maximum heart rate: 0.65×(maximum heart rate−resting heart rate)+resting heart rate. Heart rate monitors (Polar Protrainer) were provided to monitor intensity. Exercise duration was 40 minutes, including a 5-minute warm-up and cooldown.

Maximal Oxygen Consumption
Adherence to the exercise program was assessed by VO2 max and maximum workload, which were measured during a graded exercise test on an electrically braked cycle ergometer (Ergoline 900, Bitz). Workload increased at the rate of 20 W/min, with heart rate measured continuously (12-lead ECG Cardiofax V ECAPS 12, Nihon Kohden Corp) and brachial blood pressure monitored at 1-minute intervals by use of automated auscultation via a sphygmomanometer incorporated into the bicycle. Oxygen and carbon dioxide were measured by using a 2001 CAD/Net cardiopulmonary exercise system (Medical Graphics Corp). VO2 max was established by a plateau in oxygen consumption during the final 30 seconds of exercise and a respiratory exchange ratio >1.1. VO2 max was calculated as the average value over the last 30 seconds of exercise.

Resting Blood Pressure and Heart Rate
Three brachial arterial blood pressure measurements and 3 heart rate measurements were made at 3-minute intervals with the use of a vital signs monitor (1846 SX Critikon, Dinamap), with subjects remaining in the supine position in a darkened quiet room. The mean of these 3 values was taken to represent resting levels.

Systemic Arterial Compliance
Systemic arterial compliance was determined by using the method of Liu et al24 and validated in our laboratory by Cameron and Dart23 and Kingwell et al.25 This method requires measurement of carotid artery pressure by applanation tonometry with use of a Millar Mikro-Tip pressure transducer (SPT-301, Millar Instruments) and measurement of volumetric aortic flow by use of a handheld continuous wave Doppler velocimeter with a 3.5-MHz transducer (Multi-Dopplex MD1, Huntleigh Technology); 2D echocardiography was used for assessment of the left ventricular outflow tract area. Compliance is reported in arbitrary compliance units.26 Brachial pressure was obtained simultaneously and was used to calibrate the carotid artery pressure contour with the use of diastolic and mean pressures, from which carotid systolic pressure was derived.23

Pulse-Wave Velocity
PWV, which is inversely related to the square root of compliance, was measured by using applanation tonometry (SPT-301, Millar Instruments) to give a regional estimation of arterial compliance over the trunk (carotid to femoral) and lower limb (femoral to dorsalis pedis) as described previously.23,26 Directly measured carotid-to-femoral PWV assumes that at the time the pressure is measured in the carotid artery, the wave moving toward the femoral artery will have traversed the same distance. The appropriate transit distance is thus the distance between the manubrium of the sternum and the femoral artery minus the distance between the carotid sampling site and the manubrium sternum. The carotid-femoral PWV measurement thus omits the most proximal portion of the aorta.20

Aortic Input Impedance
From the pressure and flow velocity waveforms obtained for the compliance determinations, we constructed an ensemble-averaged time series and calculated aortic input and characteristic impedance, as described previously.26

Left Ventricular Structure and Function
Two-dimensional echocardiography was used to assess left ventricular dimensions, wall thickness, cardiac mass, and systolic and diastolic function. Echocardiography was performed and analyzed by an operator who was blinded to training status, as previously described.26

Biochemical Analyses
A 20-ml blood sample was taken at baseline and after each intervention for analysis of plasma LDL and HDL cholesterol and triglycerides by enzymatic analysis with use of a Cobas-BIO centrifugal analyzer (Roche Diagnostic Systems).

Statistical Analysis
All data are presented as mean±SEM, unless otherwise stated. ISH patients and control subjects were compared by using unpaired t tests. For the ISH patients who participated in the training program, ANOVA for repeated measures was used to examine the effects of training status and the order of intervention. All statistical analysis was performed by using SPSS (version 9.0, SPSS Inc).

Results
ISH Group Versus Control Group
ISH patients and control subjects did not differ with respect to age, body mass index, height, LDL and HDL cholesterol, or triglycerides (Table 1). Brachial and carotid systolic, diastolic (Figure), mean, and pulse pressures were higher in the ISH group than in the control group, whereas heart rate was not different (Table 1).
### TABLE 1. Subject Characteristics (Control Versus ISH)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Subjects</th>
<th>ISH Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.9±0.8</td>
<td>29.5±1.3</td>
<td>0.10</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168±2</td>
<td>168±2</td>
<td>0.89</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.36±0.23</td>
<td>3.25±0.09</td>
<td>0.60</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.17±0.09</td>
<td>1.26±0.09</td>
<td>0.48</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.27±0.15</td>
<td>1.62±0.21</td>
<td>0.17</td>
</tr>
<tr>
<td>Pulse pressure (brachial), mm Hg</td>
<td>53±2</td>
<td>77±3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>93±2</td>
<td>114±3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (carotid), mm Hg</td>
<td>119±3</td>
<td>154±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure (carotid), mm Hg</td>
<td>47±3</td>
<td>76±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>62±2</td>
<td>64±2</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

### Arterial Mechanics

All indices of arterial mechanics indicated that the ISH patients, compared with control subjects, had stiffer aortas. Systemic arterial compliance was lower, and input and characteristic impedance and carotid-to-femoral PWV were higher in ISH patients than in control subjects (Table 2). There was no difference in peripheral PWV between control and ISH patient groups (Table 2).

### Effects of Training in ISH Group

Consistent with adherence to the training program, VO₂max increased by 13±5% (P=0.04), and maximum workload increased by 8±4% (P=0.05), but resting heart rate did not change (Table 3) in the ISH group. Weight, HDL and LDL cholesterol, and triglycerides remained stable with the training intervention (Table 3). Brachial and carotid blood pressures did not change as a result of training (Figure), and there was no effect of training on any of the indices of arterial mechanics or left ventricular mass or function (Table 3).

### Discussion

The major finding of the present study was that moderate aerobic exercise training did not improve large-artery stiffness in patients with ISH. In support of previous studies, ISH patients had stiffer aortas than did normotensive control subjects. Although improvement in aerobic and maximum work capacity, an 8-week exercise program failed to improve resting large-arterial mechanical properties or blood pressure. Because similar exercise programs have been shown to improve both blood pressure and arterial stiffness in younger subjects, the data suggest that the large-artery stiffening associated with ISH is resistant to modification through short-term aerobic training.

Elderly athletes have a higher arterial compliance than do age-matched sedentary control subjects; however, these findings may be related to genetic, dietary, or long-term training habits and do not provide insight into the effects of training in previously sedentary patients with ISH. Although training improves arterial compliance in healthy middle-aged individuals, the effects of training in elderly ISH individuals have not been examined before. A number of studies, however, have observed reductions in mean blood pressures with low to moderate intensity training from 8 weeks to 9 months in hypertensive patients both medicated and untreated. The effect on pulse pressure was not specifically examined in these studies, but in many cases, there was little or no effect. These data, together

### TABLE 2. Arterial Mechanical Properties (Control Versus ISH)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Subjects</th>
<th>ISH Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arterial compliance, ACU</td>
<td>0.43±0.04</td>
<td>0.29±0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Input impedance, mm Hg · s · cm⁻¹</td>
<td>2.39±0.19</td>
<td>3.27±0.34</td>
<td>0.04</td>
</tr>
<tr>
<td>Characteristic impedance, mm Hg · s · cm⁻¹</td>
<td>1.67±0.17</td>
<td>2.34±0.27</td>
<td>0.05</td>
</tr>
<tr>
<td>Carotid-femoral PWV, m/s</td>
<td>9.67±0.36</td>
<td>11.43±0.51</td>
<td>0.007</td>
</tr>
<tr>
<td>Femoral-dorsalis pedis PWV, m/s</td>
<td>9.17±0.36</td>
<td>9.62±0.43</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Values are mean±SEM. ACU indicates arbitrary compliance units.

### TABLE 3. Effects of Aerobic Training in ISH Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sedentary</th>
<th>Training</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂max, mL · kg · min⁻¹</td>
<td>21.4±2</td>
<td>24.3±2</td>
<td>0.04</td>
</tr>
<tr>
<td>Wmax, W</td>
<td>138±16</td>
<td>156±21</td>
<td>0.05</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64±3</td>
<td>65±2</td>
<td>0.38</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.1±1</td>
<td>29.1±0.2</td>
<td>0.85</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.37±0.18</td>
<td>3.65±0.20</td>
<td>0.34</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.45±0.23</td>
<td>1.25±0.11</td>
<td>0.33</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.74±0.33</td>
<td>1.43±0.18</td>
<td>0.40</td>
</tr>
<tr>
<td>Systemic arterial compliance, ACU</td>
<td>0.35±0.06</td>
<td>0.38±0.06</td>
<td>0.39</td>
</tr>
<tr>
<td>Input impedance, mm Hg · s · cm⁻¹</td>
<td>2.70±0.29</td>
<td>2.75±0.39</td>
<td>0.54</td>
</tr>
<tr>
<td>Characteristic impedance, mm Hg · s · cm⁻¹</td>
<td>1.92±0.31</td>
<td>1.85±0.26</td>
<td>0.83</td>
</tr>
<tr>
<td>Carotid-femoral PWV, m/s</td>
<td>11.5±0.9</td>
<td>11.5±0.6</td>
<td>0.97</td>
</tr>
<tr>
<td>Femoral-dorsalis pedis PWV, m/s</td>
<td>9.02±0.68</td>
<td>9.23±0.81</td>
<td>0.70</td>
</tr>
<tr>
<td>Left ventricular mass, g</td>
<td>198±22</td>
<td>209±31</td>
<td>0.53</td>
</tr>
<tr>
<td>Fractional shortening, %</td>
<td>41.5±0.6</td>
<td>43.3±1.8</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Wmax indicates maximum workload.

Blood pressure for total population of control group (n=20), total population of ISH group (n=20), and ISH group after the sedentary phase (ISH Sed, n=10) and after the training phase (ISH Train, n=10) of the exercise study. The top of each bar represents SBP; the band in the middle, mean arterial pressure; and the base of each bar, DBP. Data are presented as mean±SEM. *P<0.001.
with the results of the present investigation, suggest that central arterial mechanical properties are resistant to modification by training in older populations with ISH. Much of the reduction in blood pressure observed with training in young healthy individuals is systolic and therefore probably related to increased compliance.23 Because compliance (and therefore PWV) was unchanged by training in our ISH patients, the reflected wave and systolic pressure augmentation would also be expected to remain unchanged. Furthermore, the lack of resting mean pressure reduction suggests that ISH patients are also resistant to training-induced modification of the resistance vasculature. In support of this contention, smaller muscular vessels, such as the radial artery, are also known to be stiffer in ISH patients.6,31

There are a number of mechanisms underlying arterial stiffening with age, and it is likely that these mechanisms are accelerated in ISH. These include degradation of the elastic matrix,19,20,32,33 increased smooth muscle cell content because of both hypertrophy and hyperplasia,34 and increased collagen content.35 The additional effect of prolonged high blood pressure appears to strongly hasten these age-related changes, slowing collagen turnover and causing greater stiffening of the aorta.35 Furthermore, calcium overload in a rat model has been shown to induce ISH6,37 through calcification and destruction of elastin. Interestingly, perindopril treatment was able to reverse the effects on large-artery properties but had no effect on vascular resistance. Aortic atherosclerosis also contributes to aortic stiffening. Several studies in monkeys have shown significant increases in aortic PWV that are associated with the progression of atherosclerosis,38,39 and an improvement in aortic distensibility with regression.40 In humans, Hirai et al41 showed that the distensibility of the aorta provides reliable information on the atherosclerotic damage of large arteries after myocardial infarction. The mechanisms of arterial stiffening discussed are likely to be largely irreversible and thus resistant to an 8-week training intervention despite the fact that this intervention can improve large-artery stiffness in younger normotensive individuals after only 4 weeks of training.

Study Limitations
Although 8 weeks of aerobic training did not alter either arterial mechanical properties or blood pressure in ISH patients, more intensive or longer duration training programs may have some efficacy with regard to effects on smooth muscle or atherosclerotic plaque burden42 but would not be expected to restore the elastic matrix or reverse calcification. Training earlier in life, however, may reduce age-related stiffening and prevent ISH.20,22,27

Conclusions
Arterial stiffening is resistant to modification, and blood pressure is not reduced by an 8-week home-based aerobic exercise training program in elderly patients with ISH.

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