Short-term Aerobic Exercise Reduces Arterial Stiffness in Older Adults with Type 2 Diabetes, Hypertension and Hypercholesterolemia

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**Objective:** The relationship between increased arterial stiffness and cardiovascular mortality is well established in Type 2 diabetes. We examined whether aerobic exercise could reduce arterial stiffness in older adults with Type 2 diabetes complicated by co-morbid hypertension and hyperlipidemia.

**Research design and methods:** 36 older adults (mean age 71.4±0.7) with diet-controlled or oral hypoglycemic-controlled Type 2 diabetes, hypertension, and hypercholesterolemia were recruited. Subjects were randomized to each of 2 groups: an aerobic group (AT, 3 months vigorous aerobic exercise), and a nonaerobic (NA, no aerobic exercise) group. Exercise sessions were supervised by a certified exercise trainer 3 times per week, and utilized a combination of cycle ergometers and treadmills. Arterial stiffness was measured using the Complior device.

**Results:** When the two groups were compared, aerobic training resulted in a decrease in measures of both radial (-20.7±6.3% versus +8.5±6.6%, p=0.005) and femoral (-13.9±6.7% versus +4.4±3.3%, p=0.015) pulse wave velocity despite the fact that aerobic fitness as assessed by VO$_{2\text{max}}$ (maximal oxygen consumption) did not demonstrate an improvement with training (p=0.026).

**Conclusions:** Our findings indicate that a relatively short aerobic exercise intervention in older adults can reduce multifactorial arterial stiffness (Type 2 diabetes, aging, hypertension and hypercholesterolemia).
The normal aging process is associated with an increase in vascular stiffness(1) a process that is accelerated by the presence of Type 2 diabetes(2), hypercholesterolemia(3) and hypertension(4). The relationship between increased arterial stiffness and cardiovascular mortality is well established(5). Exercise has successfully reduced vascular stiffness in young populations(6), suggesting that it could be used in older adults with Type 2 diabetes complicated by other cardiovascular risk factors.

Previous cross-sectional studies have shown that older adults who engage in regular aerobic exercise training have lower arterial stiffness than sedentary older adults(7). Prospective examinations of a moderate aerobic exercise program in middle-aged subjects with Type 2 diabetes(6) and normal older adults(7) have demonstrated a decrease in arterial stiffness. In fact, even brief aerobic interventions in healthy middle-aged men have demonstrated a direct impact on arterial compliance without any effect on cholesterol, blood pressure, body weight or resting heart rate(7). It has been hypothesized that mechanical distension during aerobic exercise sessions results in pulsatile “stretching” of the collagen fibers that reverses the glycation-related collagen cross-linking that is responsible for reduced arterial compliance in diabetes(8). The impact of aerobic exercise on arterial stiffness in older adults with extensive vascular damage due to multiple etiologies (Type 2 diabetes, hypercholesterolemia, hypertension) has not been previously examined.

In the current study, we examined whether aerobic exercise can reverse arterial stiffness in adults at very high cardiovascular risk (long-standing diabetes, geriatric age group, hypercholesterolemia, and hypertension). We hypothesized that despite these multifactorial reasons for reduced arterial compliance, aerobic exercise would be an effective nonpharmacological therapy for increased arterial stiffness.

RESEARCH DESIGN AND METHODS

Subjects (Table 1): Forty older adults (21 males and 19 females, mean age 71.4±0.7, ranging in age from 65 to 83) were recruited from the local community through advertisement in local publications. All subjects had to be over 65 years of age and were excluded if they had any history of angina, myocardial infarction, stroke, chronic pulmonary disease, current smoking, or exercise-limiting orthopedic impairment. All older subjects were required to have Type 2 diabetes for at least 5 years, hypertension and hyperlipidemia. Hypertension, diabetes and hyperlipidemia were defined by current ADA guidelines(9). Hypertension was defined as taking antihypertensive agents or having an average blood pressure (based on the mean of three measurements) with a systolic blood pressure greater than 130 mm Hg or a diastolic blood pressure greater than 80 mm Hg(9). Subjects were excluded if they took beta-blockers, calcium channel blockers, or any other agent that influenced autonomic function. Entry requirements included a normal resting ECG, a normal Bruce protocol treadmill maximal exercise stress test, a normal hematocrit, and a normal creatinine. Subjects had to be sedentary at the start of the study (as defined as no strength training and less than 30 minutes brisk walking/moderate exercise per week and no vigorous exercise in the preceding 6 months). Four subjects were excluded (2 male, 2 female) on the basis of this screening, leaving a total of 36 subjects participating in the study. Eighteen subjects were randomized to each of two groups: an aerobic group (AT), and a nonaerobic (NA) group. Allocation concealment was maintained through the use of an off-site randomized list, managed by an individual that had no contact with subjects prior to completion of recruitment and screening.
This study was approved by the Human Subjects Committee of the University of British Columbia, and all subjects gave written informed consent.

**Study Design:** Each subject underwent two evaluation sessions before and after the three-month intervention. Post-intervention study sessions could be delayed up to 7 days to accommodate each subject’s schedule. All study sessions were performed with the subject supine and took place between 7 AM and noon for all subjects to avoid bias due to circadian rhythms. The technician responsible for performing all measures was blinded to subject group.

**Training Program:** The endurance training (AT group) intervention was designed to improve aerobic fitness according to current guidelines(10), and consisted of moderate to vigorous intensity exercise on a treadmill and a cycle ergometer. Training sessions were three times per week, and subjects had to attend 90% of all training sessions to remain enrolled in the study. The aerobic training sessions were 60 minutes in duration and consisted of 10 minutes warm-up, 40 minutes aerobic training and 10 minutes of cooldown/stretching. A clinical exercise physiologist supervised each class, and verified compliance with the exercise regime. Moderate to vigorous intensity exercise was attained via continuous monitoring of heart rates Polar Vantage Heart Watches (Adelaide, Australia). Based on the resting heart rate and maximal heart rate determined during maximal exercise treadmill testing (see below) we set training heart rate to 60-75% of heart rate reserve based on the Karvonen formula(11).

Subjects in the NA group also attended sessions 3 times per week. The NA group sessions were specifically designed to have no aerobic component, and consisted of nonstrenuous core (exercise ball) and nonstrenuous strength training (very light dumbbells) exercises. We confirmed a lack of aerobic training in the NA group with a test of maximal oxygen consumption in each subject(VO2max, see below). The trainer also contacted each subject weekly to ensure they were not undertaking any additional exercise. For ethical reasons, each subject in the NA group was given the option of joining the aerobic exercise group after the 3-month intervention period was complete, to encourage them to increase their level of physical fitness.

Exercise classes were held in a hospital-based facility (Healthy Heart Program, St. Paul's Hospital, Vancouver, Canada) under supervision of clinical exercise physiologists with cardiology and emergency services available. Cardiovascular measures were taken before, during and after exercise, and included blood pressure, heart rate, and blood glucose. Electrocardiogram telemetry was also available if necessary if unusual heart rate or rhythms were noted.

**Data Collection and Processing:** Subject conditions were standardized according to established guidelines: all measures were performed after 30 minutes supine rest; the environment was quiet and temperature controlled (25 ± 1 C); all subjects were fasting; and all subjects had refrained from the consumption of alcohol or caffeine for the preceding 24 hours. To avoid the confounding acute effects of exercise the aerobic training program was also halted for the preceding 24 hours(12). Arterial stiffness was measured using the Complior device (Artech Medical, Pantin, France), a semi-automated device that uses two pressure transducers(12). The pressure transducers are held in place by velcro straps that allow them to be fixed over the skin. Each pressure transducer measures the pulse waveform at each site, allowing one to measure transit time of the pulse wave between the two locations. A higher pulse wave velocity (PWV) represents greater arterial stiffness. The transducers are placed over the carotid and
femoral arteries for a measure of central arterial stiffness and over the carotid and radial arteries for a measure of peripheral arterial stiffness(12). Pulse wave velocity was calculated from these transducer measures which are digitally recorded (sampling rate 500 Hz), resulting in measures of radial and femoral PWV. Pulse wave velocity was chosen as our measure of arterial stiffness due to the fact that it is the most commonly used measure both in the literature and in consensus statements(13). Femoral PWV is also one of the only indicies of arterial stiffness directly linked with cardiovascular mortality and morbidity(14).

Heart rate (HR), systolic (SBP), diastolic (DBP) and mean (MAP) blood pressure were measured using an automated blood pressure cuff (BpTRU Medical Devices, Coquitlam, Canada). Each subject’s weight was measured using a physician’s balance scale. Body mass index, waist circumference, hip circumference and hip to waist ratio were measured and calculated as per established guidelines(15). VO$_{2\text{max}}$ was determined using a maximal Bruce treadmill protocol exercise test. The change in VO$_{2\text{max}}$ was examined in all groups, including the untrained and strength trained subjects.

**Statistical Analysis:** All data analysis was done in a blinded fashion. Results are expressed as the mean ± standard error. Our sample size calculations for our three primary outcome measures (radial PWV, femoral PWV, and VO$_{2\text{max}}$) assumed a power of 90% and a 1.66% level of significance (after a Bonferroni correction for multiple comparisons). We found that we required a sample size of at least 15 subjects to detect a 15 percent difference in our primary outcome measures. The effects of training on all measures were calculated by a two-way analysis of variance for repeated measures (time*group). The interaction of gender with training effects was examined by a three-way analysis of variance for repeated measures (time*group*gender)(16). A value of p<0.0166 was considered significant, due to a Bonferroni correction for multiple comparisons(16). Dropouts were handled on an intention-to-treat basis.

**RESULTS**

**Subject Characteristics (Table 1):** There were 2 drop-outs from the study, one from each group (a total of 34 subjects completed the intervention). One drop-out (AT group) was handled on an intent-to-treat basis, while the other (NA group) was lost to follow-up. Other than the drop-outs mentioned above, all the remaining 34 subjects attended at least 90% of the training sessions. Therefore 17 subjects from the AT group and 17 from the NA group completed the intervention. As shown in Table 1, at the time of entry into the study, there was no significant difference between AT and NA subjects with respect to demographic data, resting heart rate, resting blood pressure, fasting blood sugar, glycosylated hemoglobin or lipid profile (See Table 1).

**Effects of Training on Measures of Arterial Stiffness (Figure 1):** As shown in Figure 1, aerobic training resulted in a decrease in both radial (p=0.005) and femoral (p=0.015) PWV that was not demonstrated in the nonaerobic group. In fact, aerobic training resulted in approximately a 20.7±6.3% decrease in rPWV and 13.9±6.7% decrease in fPWV over three months. By comparison, the NA group demonstrated an 8.5±6.6% increase in radial PMV and a 4.4±3.3% increase in femoral PWV.

Male subjects in the AT group demonstrated an 25.5±9.8% decrease in radial PMV and a 15.1±7.7% decrease in femoral PWV, while female subjects in the AT group demonstrated an 18.6±8.3% decrease in radial PMV and a 12.6±6.6% decrease in femoral PWV. In the NT group, male subjects demonstrated an 9.0±11.0% increase in radial PMV and a 11.5±11.0% increase in femoral
PWV; female subjects in the NT group demonstrated an 4.1±10.5% decrease in radial PWV and a 1.8±2.3% increase in femoral PWV. There was no significant interaction of gender (time*group*gender) with the effects of training on radial (p=0.731) and femoral (p=0.260) PWV.

**Effects of Training on Measures of Fitness (Table 2 and Figure 2):** The 3-month training program did not result in a significant increase in VO\textsubscript{2max} (Figure 2, p=0.026). As shown in Table 2, there was no significant difference between the NA and AT group with respect to changes in weight (p=0.942), body mass index (p=0.396), waist-to-hip ratio (p=0.786) or fasting blood glucose (p=0.098). There was no significant difference between the two groups with respect to changes in SBP (p=0.171), MAP (p=0.078), DBP (p=0.091) or resting HR (p=0.073). There was also no significant interaction of gender (time*group*gender) with the effects of training on weight, body mass index, blood pressure, baseline heart rate and fasting blood glucose (Table 2).

**CONCLUSIONS**
Aerobic training reversed multifactorial (geriatric age, Type 2 diabetes, hypertension, hypercholesterolemia) arterial stiffness, as shown by significant decreases in both radial and femoral PWV. Improvements in arterial stiffness occurred with only 3 months of aerobic training despite the fact that this was in a population at quite high cardiovascular risk. Interestingly, this improvement occurred without any significant improvements in aerobic fitness, weight, body mass index, waist-to-hip ratio or blood pressure. This indicates that the effects of aerobic training on the vasculature may be independent of these other well-established benefits of exercise.

Previous work on the effects of aerobic exercise on arterial compliance has consisted of cross-sectional data(7), prospective interventions in young athletes(6), and prospective interventions in middle-aged healthy persons(17). Cross sectional studies of older healthy adults have shown that those who perform regular aerobic exercise have lower arterial stiffness than sedentary older adults(7). High intensity exercise (running, 6 weeks) has been shown to reduce arterial stiffness prospectively in young athletes(6). More moderate training (daily walking, 3 months) has been shown prospectively to improve arterial compliance in middle-aged healthy women by about 40 percent, similar to the present study(17). Congruent with the results of the present study, brief (3 months walking) aerobic interventions in healthy middle-aged men (mean age 52 years) have demonstrated reductions in arterial stiffness without any effect on cholesterol, blood pressure, body weight or resting heart rate(7). A combined nutrition and walking program(18) as well as a pure walking intervention(6) have also demonstrated prospectively a decrease in arterial stiffness in the middle-aged Type 2 diabetes population. To our knowledge, our study is the first to show that even older adults at very high cardiovascular risk due to Type 2 diabetes, age, hypertension and hypercholesterolemia can reduce arterial stiffness with regular aerobic exercise.

The normal aging process is associated with an increase in vascular stiffness(19), a process that is accelerated by the presence of Type 2 diabetes(2). The normal process of aging is known to result in increased arterial stiffness due to an increase in intima and media thickness, smooth muscle cell hyperplasia, and extracellular matrix proliferation. Diabetes has been shown to accelerate this age-associated stiffening(20) mainly through non-enzymatic glycation, the reaction between glucose and the extracellular matrix proteins in the arterial wall. Non-enzymatic glycation leads to the formation of increased collagen crosslinks that result in
increased arterial stiffness(21). It has been theorized that pulsatile stretching of collagen fibers during aerobic exercise can break these collagen crosslinks, resulting in a decrease in arterial stiffness(8). Interestingly, the fact that we did not demonstrate a significant change in VO$_{2\text{max}}$ suggests that this decrease in arterial stiffness can occur even in the absence of an improvement in overall aerobic fitness (Figure 2). Aerobic exercise has also been shown to increase arterial elastin content and decrease calcium content in rats(22), although the role for this mechanism in humans remains uncertain and is unlikely to be a factor during a 3-month intervention.

**Clinical Implications:** In persons with diabetes, previous research has strongly established the relationship between vascular stiffness and cardiovascular mortality(5). Our study population consisted of older subjects with Type 2 diabetes complicated by co-morbid hypertension, and hyperlipidemia, putting them at very high risk for arterial stiffness and the consequent cardiovascular risks associated with this condition. Despite having multiple cardiovascular risk factors, we were able to show a significant decrease in both radial and femoral PWV. This is especially important with respect to femoral PWV, one of the few measures directly linked with cardiovascular mortality and morbidity(14). Although there have been some proposed pharmacological treatments for arterial stiffness(23), the results of the current study indicates that aerobic exercise should be first-line treatment to reduce arterial stiffness in older adults with Type 2 diabetes, even if the patient has additional cardiovascular risk factors such as hypertension and hypercholesterolemia.

**Limitations:** Further research is needed to determine the pathophysiological mechanism for the reduction in radial and femoral PWV with aerobic exercise in our population. We also do not know if the observed improvements in arterial stiffness with aerobic exercise persist over longer periods of time, since our subjects were only examined during the 3 month training period.

Our study was unable to detect any significant training effect on weight, BMI, waist circumference and fasting blood glucose. The main reason for this is that our study was only powered to detect three primary outcome measures (radial PWV, femoral PWV, and VO$_{2\text{max}}$). However, since female gender has been associated with lower aerobic endurance in subjects with Type 2 diabetes(24) there is the possibility that a significant training effect was obscured by gender differences. Congruent with the most recent meta-analysis literature(25), we did not detect any significant interaction between gender and the effects of training on weight, BMI, waist circumference and fasting blood glucose (Table 2). This observed lack of a gender effect needs to be interpreted with caution since our study had insufficient numbers to adequately assess gender-differences in the training response.

Since our exercise intervention was completed by a relatively small sample size, the benefits of aerobic training on arterial stiffness need to be confirmed by larger studies. The fact that a short 3-month intervention produced a sizable decrease in arterial stiffness suggests that larger exercise studies in this high-risk group are practicable and might be able to demonstrate training-induced improvements in mortality or cardiovascular event rates.

**Summary:** We demonstrated that aerobic exercise reduces multifactorial (Type 2 diabetes, aging, hypertension and hypercholesterolemia) arterial stiffness with a relatively short intervention. Aerobic exercise should be first line therapy for arterial stiffness, regardless of the underlying etiology.

**ACKNOWLEDGEMENTS**
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REFERENCES


Table 1—Subject Characteristics

<table>
<thead>
<tr>
<th>Measure</th>
<th>All subjects</th>
<th>AT Subjects</th>
<th>NA Subjects</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.4±0.7</td>
<td>71.7±1.1</td>
<td>71.1±0.9</td>
<td>0.417</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.3±2.1</td>
<td>81.9±2.2</td>
<td>79.3±3.1</td>
<td>0.554</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.6±1.5</td>
<td>165.4±2.1</td>
<td>169.0±2.1</td>
<td>0.263</td>
</tr>
<tr>
<td>Body Mass Index (kg/m$^2$)</td>
<td>28.6±0.64</td>
<td>30.1±1.1</td>
<td>27.7±1.0</td>
<td>0.064</td>
</tr>
<tr>
<td>Waist to Hip Ratio</td>
<td>0.95±0.01</td>
<td>0.96±0.02</td>
<td>0.94±0.02</td>
<td>0.315</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>143±3</td>
<td>150±6</td>
<td>139±4</td>
<td>0.149</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>85±2</td>
<td>83±2</td>
<td>86±2</td>
<td>0.329</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>104±2</td>
<td>105±3</td>
<td>104±3</td>
<td>0.723</td>
</tr>
<tr>
<td>Heart Rate (beats per minute)</td>
<td>66.0±2.2</td>
<td>66.8±4.1</td>
<td>65.3±2.3</td>
<td>0.744</td>
</tr>
<tr>
<td>Fasting Blood Glucose (mEq)</td>
<td>7.5±0.3</td>
<td>7.9±0.6</td>
<td>7.1±0.3</td>
<td>0.22</td>
</tr>
<tr>
<td>Glycosylated Hemoglobin (%)</td>
<td>6.5±0.1</td>
<td>6.7±0.2</td>
<td>6.4±0.1</td>
<td>0.432</td>
</tr>
<tr>
<td>Total Cholesterol (mmol / L)</td>
<td>4.7±0.2</td>
<td>5.0±0.2</td>
<td>4.6±0.3</td>
<td>0.290</td>
</tr>
<tr>
<td>LDL Cholesterol (mmol / L)</td>
<td>2.6±0.2</td>
<td>2.6±0.8</td>
<td>2.5±0.2</td>
<td>0.592</td>
</tr>
<tr>
<td>HDL Cholesterol (mmol / L)</td>
<td>1.5±0.1</td>
<td>1.5±0.1</td>
<td>1.5±0.1</td>
<td>0.619</td>
</tr>
<tr>
<td>Radial PWV (m/s)</td>
<td>10.08±0.34</td>
<td>10.41±0.58</td>
<td>9.65±0.60</td>
<td>0.368</td>
</tr>
<tr>
<td>Femoral PWV (m/s)</td>
<td>11.97±0.44</td>
<td>12.68±0.76</td>
<td>11.17±0.75</td>
<td>0.163</td>
</tr>
</tbody>
</table>

Demographic data for aerobically trained (AT), untrained (NA) and all subjects are shown as mean±standard error. A p-value of < 0.05 was considered significant. SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MAP, Mean arterial pressure; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; PVM, Pulse wave velocity
Table 2—Change in Fitness Measures After Intervention

<table>
<thead>
<tr>
<th>Measure</th>
<th>Delta for AT Subjects</th>
<th>Delta for NA Subjects</th>
<th>P value (time*group)</th>
<th>P value (time<em>group</em>gender)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>+0.082±0.732</td>
<td>+0.140±0.364</td>
<td>0.942</td>
<td>0.103</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.23±0.28</td>
<td>+0.05±0.17</td>
<td>0.396</td>
<td>0.137</td>
</tr>
<tr>
<td>WHR</td>
<td>-0.002±0.007</td>
<td>0.002±0.011</td>
<td>0.786</td>
<td>0.854</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>-10±5</td>
<td>-2±3</td>
<td>0.171</td>
<td>0.567</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>-5±2</td>
<td>-1±2</td>
<td>0.091</td>
<td>0.396</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>-7±3</td>
<td>-1±3</td>
<td>0.078</td>
<td>0.906</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>-5.4±2.7</td>
<td>-0.4±1.1</td>
<td>0.073</td>
<td>0.103</td>
</tr>
<tr>
<td>FBG (mEq)</td>
<td>-0.8±0.3</td>
<td>-0.1±0.2</td>
<td>0.098</td>
<td>0.698</td>
</tr>
</tbody>
</table>

Changes in measures of fitness for aerobically trained (AT) and untrained (NA) are shown as mean±standard error. None of these measures showed a significant training effect (time*group) due to the fact that our study was only powered to find an effect for our three primary outcomes. There was also no significant interaction of gender (time*group*gender) with the effects of training. BMI, Body mass index; WHR, Waist to hip ratio; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MAP, Mean arterial pressure; HR, Heart rate; bpm, beats per minute; FBG, Fasting blood glucose
FIGURE CAPTIONS

1. Aerobic training (AT) resulted in a decrease in both radial (rPWV, p=0.005) and femoral (fPWV, p=0.015) pulse wave velocity that was not demonstrated in the nonaerobic (NA) group. Black = AT group; White = NA group.

2. The three month training program did not result in a significant increase in VO\textsubscript{2max} (p=0.026). Black = AT group; White = NA group.