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 comorbid hypertension and hyperlipidemia.

RESEARCH DESIGN AND METHODS — A total of 36 older adults (mean age 71.4 ± 0.7 years) with diet-controlled or oral hypoglycemic–controlled type 2 diabetes, hypertension, and hypercholesterolemia were recruited. Subjects were randomly assigned to one of two groups: an aerobic group (3 months vigorous aerobic exercise) and a nonaerobic group (no aerobic exercise). Exercise sessions were supervised by a certified exercise trainer three times per week, and a combination of cycle ergometers and treadmills was used. 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 vs. +8.5 ± 6.6%, $P = 0.005$) and femoral (−13.9 ± 6.7 vs. +4.4 ± 3.3%, $P = 0.015$) pulse-wave velocity despite the fact that aerobic fitness as assessed by $V_{O_{2max}}$ 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).

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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, and hypertension) has not been examined previously.

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

— Forty older adults (21 men and 19 women, mean age 71.4 ± 0.7 years, age range from 65 to 83 years) were recruited from the local community through advertisement in local publications (Table 1). All subjects had to be aged >65 years and were excluded if they had any history of angina, myocardial infarction, stroke, chronic pulmonary disease, were current smokers, or had 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 American Diabetes Association 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 >130 mmHg or a diastolic blood pressure >80 mmHg (9).

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Table 1—*Subject characteristics*

	All subjects	AT subjects	NA subjects	*P*
Age (years)	71.4 ± 0.7	71.7 ± 1.1	71.1 ± 0.9	0.417
Weight (kg)	80.3 ± 2.1	81.9 ± 2.2	79.3 ± 3.1	0.554
Height (cm)	167.6 ± 1.5	165.4 ± 2.1	169.0 ± 2.1	0.263
BMI (kg/m^2)	28.6 ± 0.64	30.1 ± 1.1	27.7 ± 1.0	0.064
Waist-to-hip ratio	0.95 ± 0.01	0.96 ± 0.02	0.94 ± 0.02	0.315
SBP (mmHg)	143 ± 3	150 ± 6	139 ± 4	0.149
DBP (mmHg)	85 ± 2	83 ± 2	86 ± 2	0.329
MAP (mmHg)	104 ± 2	105 ± 3	104 ± 3	0.723
Heart rate (bpm)	66.0 ± 2.2	66.8 ± 4.1	65.3 ± 2.3	0.744
Fasting blood glucose (mEq)	7.5 ± 0.3	7.9 ± 0.6	7.1 ± 0.3	0.22
A1C (%)	6.5 ± 0.1	6.7 ± 0.2	6.4 ± 0.1	0.432
Total cholesterol (mmol/l)	4.7 ± 0.2	5.0 ± 0.2	4.6 ± 0.3	0.290
LDL cholesterol (mmol/l)	2.6 ± 0.2	2.6 ± 0.8	2.5 ± 0.2	0.592
HDL cholesterol (mmol/l)	1.5 ± 0.1	1.5 ± 0.1	1.5 ± 0.1	0.619
Radial PWV (m/s)	10.08 ± 0.34	10.41 ± 0.58	9.65 ± 0.60	0.368
Femoral PWV (m/s)	11.97 ± 0.44	12.68 ± 0.76	11.17 ± 0.75	0.163

Data are means ± SEM. Demographic data for aerobically trained (AT), untrained (NA), and all subjects. $P < 0.05$ was considered significant.

Subjects were excluded if they took β-blockers, calcium channel blockers, or any other agent that influenced autonomic function. Entry requirements included a normal resting electrocardiogram, a normal Bruce protocol treadmill maximal exercise stress test, a normal hematocrit, and a normal creatinine level. Subjects had to be sedentary at the start of the study (as defined as no strength training and >30 min brisk walking/moderate exercise per week and no vigorous exercise in the preceding 6 months). Four subjects were excluded (two male and two female) on the basis of this screening, leaving a total of 36 subjects participating in the study. Eighteen subjects were randomly assigned to each of two groups: an aerobic group and a nonaerobic group. Allocation concealment was maintained through the use of an off-site randomized list, managed by an individual who had no contact with subjects before 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.

Each subject underwent two evaluation sessions before and after the 3-month intervention. Postintervention 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 7:00 A.M. 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 (aerobic 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 conducted 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 min in duration and consisted of a 10-min warm-up, 40 min of aerobic training, and 10 min of cool down/stretching. A clinical exercise physiologist supervised each class and verified compliance with the exercise regimen. Moderate to vigorous intensity exercise was attained via continuous monitoring of heart rates (Polar Vantage Heart Watches; Pursuit Performance, Adelaide, Australia). Based on the resting heart rate and maximal heart rate determined during maximal exercise treadmill testing (see below), we set the training heart rate to 60–75% of heart rate reserve based on the Karvonen formula (11).

Subjects in the nonaerobic group also attended sessions three times per week. The nonaerobic group sessions were specifically designed to have no aerobic component and consisted of nonaerobic core (exercise ball) and strength training (dumbbells) exercises. We confirmed a lack of aerobic training in the nonaerobic group with a test of maximal oxygen consumption in each subject($V_{O_{2max}}$, see below). The trainer also contacted each subject weekly to ensure that he or she was not undertaking any additional exercise. For ethical reasons, all subjects in the nonaerobic 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, BC, Canada) under the supervision of clinical exercise physiologists with cardiology and emergency services available. Cardiovascular measurements were taken before, during, and after exercise and included blood pressure, heart rate, and blood glucose. Electrocardiogram telemetry was also available, if necessary, when unusual heart rates or rhythms were noted.

Data collection and processing

Subject conditions were standardized according to established guidelines: all measurements were performed after 30 min of supine rest, the environment was quiet and temperature controlled (25 ± 1°C), all subjects were fasting, and all subjects had refrained from consumption of alcohol or caffeine for the preceding 24 h. To avoid the confounding acute effects of exercise, the aerobic training program was also halted for the preceding 24 h (12). Arterial stiffness was measured using the Complior device (Artech Medical, Pantin, France), a semiautomated device that uses two pressure transducers (12). The pressure transducers are held in place by Velcro straps that allow them be fixed over the skin. Each pressure transducer measures the pulse-wave form 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). PWV was calculated from these transducer measures, which are digitally recorded (sampling rate 500 Hz), resulting in measures of radial and femoral PWV. PWV was chosen as our measure of arterial stiffness because it is the most commonly used measure both in the literature and in consensus statements (13). Femoral PWV is also one of the only indexes of arterial stiffness directly linked with cardiovascular mortality and morbidity (14).

Heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean (MAP) blood pressure were

measured using an automated blood pressure cuff (BpTRU Medical Devices, Coquitlam, BC, Canada). Each subject's weight was measured using a physician's balance scale. BMI, waist circumference, hip circumference, and waist-to-hip ratio were measured and calculated as per established guidelines (15). $V_{O_{2max}}$ was determined using a maximal Bruce treadmill protocol exercise test. The change in $V_{O_{2max}}$ 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 means ± SEM. Our sample size calculations for our three primary outcome measures (radial PWV, femoral PWV, and $V_{O_{2max}}$) 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% difference in our primary outcome measures. The effects of training on all measures were calculated by a two-way ANOVA for repeated measures (time × group). The interaction of sex with training effects was examined by a three-way ANOVA for repeated measures (time × group × sex) (16). A value of $P < 0.0166$ was considered significant, because of a Bonferroni correction for multiple comparisons (16). Dropouts were handled on an intention-to-treat basis.

RESULTS

Subject characteristics

There were two dropouts from the study, one from each group (a total of 34 subjects completed the intervention). One dropout (aerobic group) was handled on an intent-to-treat basis, whereas the other (nonaerobic group) was lost to follow-up. Other than the dropouts mentioned above, all of the remaining 34 subjects attended at least 90% of the training sessions. Therefore, 17 subjects from the aerobic group and 17 from the nonaerobic group completed the intervention. As shown in Table 1, at the time of entry into the study, there was no significant difference between aerobic and nonaerobic group subjects with respect to demographic data, resting heart rate, resting blood pressure, fasting blood glucose, A1C, or lipid profile.

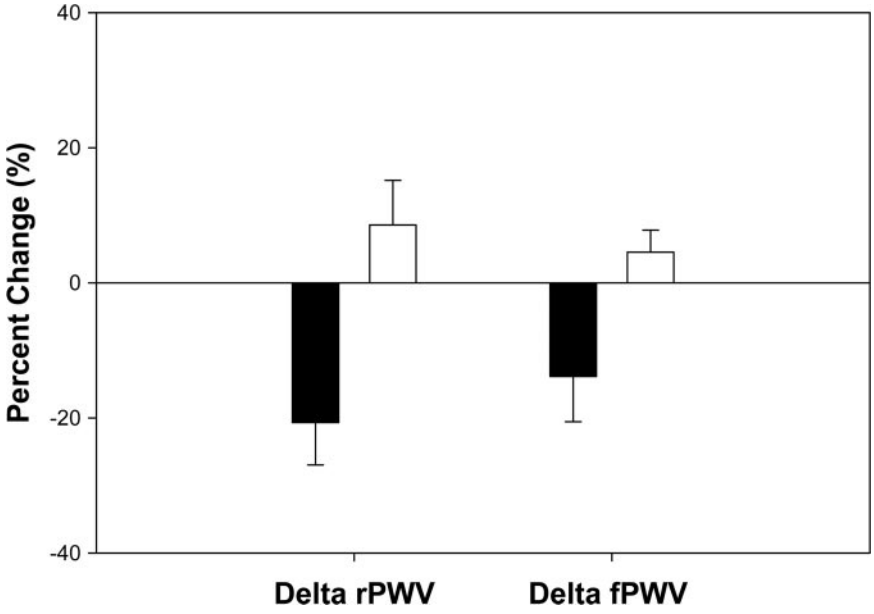

Figure 1—*Aerobic training (AT, ■) resulted in a decrease in both radial PWV (rPWV) (P = 0.005) and femoral PWV (fPWV) (P = 0.015) that was not demonstrated in the nonaerobic (NA, □) group.*

Effects of training on measures of arterial stiffness

As shown in Fig. 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 an ~20.7 ± 6.3% decrease in radial PWV and a 13.9 ± 6.7% decrease in femoral PWV over 3 months. In comparison, the nonaerobic 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 aerobic group demonstrated a 25.5 ± 9.8% decrease in radial PMV and a 15.1 ± 7.7% decrease in femoral PWV, whereas female subjects in the aerobic training group demonstrated an 18.6 ± 8.3% decrease in radial PMV and a 12.6 ± 6.6% decrease in femoral PWV. In the nonaerobic group, male subjects demonstrated a 9.0 ± 11.0% increase in radial PMV and an 11.5 ± 11.0% increase in femoral PWV; female subjects in the nonaerobic group demonstrated an 4.1 ± 10.5% decrease in radial PMV and a 1.8 ± 2.3% increase in femoral PWV. There was no significant interaction of sex (time × group × sex) with the effects of training on radial ($P = 0.731$) and femoral ($P = 0.260$) PWV.

Effects of training on measures of fitness

The 3-month training program did not result in a significant increase in $V_{O_{2max}}$ (Fig. 2) ($P = 0.026$). As shown in Table 2, there was no significant difference between the nonaerobic and aerobic groups with respect to changes in weight ($P = 0.942$), BMI ($P = 0.396$), 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 heart rate ($P = 0.073$). There was also no significant interaction of sex (time × group × sex) with the effects of training on weight, BMI, blood pressure, baseline heart rate, and fasting blood glucose (Table 2).

CONCLUSIONS — Aerobic training reversed multifactorial (geriatric age, type 2 diabetes, hypertension, and 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, BMI, waist-to-hip ratio, or blood pressure. This finding 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), pro-

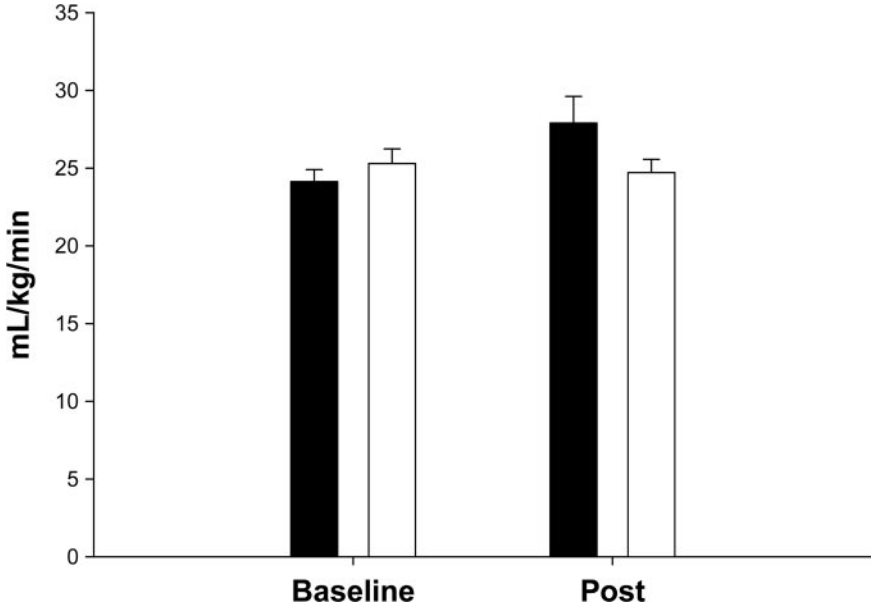

Figure 2—*The 3-month training program did not result in a significant increase in* VO_{2max} *(P = 0.026) in the aerobic group (AT, ■) or nonaerobic (NA, □)group.*

spective interventions in young athletes (6), and prospective interventions in middle-aged heathy 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 ~40%, similar to the present study (17). Congruent with the results of the present study, brief (3 months of 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 diabetic population. To our knowledge, our study is the first to show that even in older adults at very high cardiovascular risk due to type 2 diabetes, age, hypertension, and hypercholesterolemia arterial stiffness can be reduced 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 because of 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 nonenzymatic glycation, the reaction between glucose and the extracellular matrix proteins in the arterial wall. Nonenzymatic 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_{2max} suggests that this decrease in arterial stiffness can occur even in the absence of an improvement in overall aerobic fitness (Fig. 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 comorbid 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 indicate that aerobic exer-

Table 2 —*Change in fitness measures after intervention*

	Δ for AT subjects	Δ for NA subjects	*P* (time × group)	*P* (time × group × sex)
Weight (kg)	+0.082 ± 0.732	+0.140 ± 0.364	0.942	0.103
BMI (kg/m^2)	−0.23 ± 0.28	+0.05 ± 0.17	0.396	0.137
Waist-to-hip ratio	−0.002 ± 0.007	0.002 ± 0.011	0.786	0.854
SBP (mmHg)	−10 ± 5	−2 ± 3	0.171	0.567
DBP (mmHg)	−5 ± 2	−1 ± 2	0.091	0.396
MAP (mmHg)	−7 ± 3	−1 ± 3	0.078	0.906
Heart rate (bpm)	−5.4 ± 2.7	−0.4 ± 1.1	0.073	0.103
Fasting blood glucose (mEq)	−0.8 ± 0.3	−0.1 ± 0.2	0.098	0.698

Data are means ± SEM. Changes in measures of fitness for aerobically trained (AT) and untrained (NA) subjects are shown. None of these measures showed a significant training effect (time × group) because our study was only powered to find an effect for our three primary outcomes. There was also no significant interaction of gender (time × group × sex) with the effects of training.

cise should be the 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, because 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 is that our study was only powered to detect three primary outcome measures (radial PWV, femoral PWV, and $V\text{O}_{2max}$). However, because female sex 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 sex differences. Congruent with the most recent meta-analysis literature (25), we did not detect any significant interaction between sex and the effects of training on weight, BMI, waist circumference, and fasting blood glucose (Table 2). This observed lack of a sex effect needs to be interpreted with caution because our study had insufficient numbers to adequately assess sex differences in the training response.

Because our exercise intervention was completed by a relatively small number of subjects, 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.

In 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.

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No potential conflicts of interest relevant to this article were reported.

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