Short-term Aerobic Exercise Reduces Nitroglycerin-induced Orthostatic Intolerance in Older Adults With Type 2 Diabetes

Kenneth M. Madden, MD, Chris K. Lockhart, BSc, Tiffany F. Potter, PhD, Darcye J. Cuff, PhD, and Graydon S. Meneilly, MD

VITALITY (Vancouver Initiative to Add Life to Years) Research Laboratory, Division of Geriatric Medicine, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

Abstract

Aims/Hypothesis—Older adults are at a high risk for syncope due to orthostatic intolerance (OI), and this risk increases with comorbid type 2 diabetes and vasoactive medications. Despite many benefits, previous investigations have shown worsening OI with aerobic training. We examined whether aerobic exercise reduced OI in older adults with type 2 diabetes who were given a short-acting vasoactive agent (nitroglycerin).

Methods—Forty older adults (25 males and 15 females, mean age 71.4 ± 0.7 years, ranging in age from 65 to 83 years) with type 2 diabetes were recruited. Subjects were randomized to each of 2 groups: an aerobic group (3 months of vigorous aerobic exercise) and a nonaerobic (no aerobic exercise) group. Exercise sessions were supervised by a certified exercise trainer 3 times per week. After being given 400 μ g of sublingual nitroglycerin, each subject was placed in a 70° head-up tilt for 30 minutes.

Results—When the 2 groups were compared using a Cox proportional hazards model, tilt table tolerance was significantly better in the aerobic group as compared to in the nonaerobic group ($\chi^2_{MC} = 7.271$, $P = 0.007$).

Conclusions—Our findings indicate that a relatively short aerobic exercise intervention can improve postnitroglycerin orthostatic tolerance in older adults with type 2 diabetes.

Keywords

type 2 diabetes; gerontology; aerobic exercise; orthostatic intolerance

INTRODUCTION

Syncope due to orthostatic hypotension (OH) is common in the elderly: An examination of nationwide discharge data in the United States has demonstrated a rate of annual hospitalization of 233 per 100,000 in older adults.¹ The presence of type 2 diabetes in older

Reprints: Kenneth M. Madden, MD, Room 7185, Gordon and Leslie Diamond Health Care Centre, 2775 Laurel St, Vancouver, BC, Canada V5Z 1M9 (kmmadden@interchange.ubc.ca).

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adults has been associated with syncope due to OH¹ and will increase chances of fainting by 30%.² The most common medication-related predictor of OH-induced syncope has been shown to be nitroglycerin (GTN).³ Our study sought to examine the ability of aerobic exercise to improve orthostatic tolerance while taking GTN in older adults with type 2 diabetes.

Impaired arterial baroreflex function has been shown to be predictive of poor tolerability of vasodilatory medications in older adults⁴ suggesting that improving arterial baroreflex sensitivity with exercise⁵ could potentially improve orthostatic tolerance to GTN in this vulnerable population. Vigorous aerobic training has been shown to improve orthostatic tolerance in young normal subjects,⁶ but some investigations have demonstrated a worsening⁷⁻⁹ or no¹⁰ effect of aerobic training on orthostatic tolerance. The impact of aerobic exercise on GTN-induced orthostatic intolerance in older adults with type 2 diabetes has not been previously examined.

In this study, we examined whether aerobic exercise can improve orthostatic tolerance to GTN in adults with type 2 diabetes. We hypothesized that aerobic exercise would be an effective nonpharmacological therapy to improve orthostatic tolerance to GTN.

METHODS

Subjects

This study was approved by the Human Subjects Committee of the University of British Columbia, and all subjects gave written informed consent.

Forty-six older adults (28 males and 18 females) were recruited from the local community through advertisement in local publications. All subjects had to be older than 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. Diabetes was defined by current American Diabetes Association guidelines.¹¹ Entry requirements included a normal resting electrocardiogram, 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 <30 minutes of brisk walking/moderate exercise per week and no vigorous exercise in the preceding 6 months). Due to safety issues with upright aerobic training, subjects with significant OH [defined as a drop in systolic blood pressure (SBP) >30 mm Hg immediately after changing position from lying to standing] were excluded. Four subjects were excluded (2 male, 2 female) on the basis of this screening, leaving a total of 42 subjects participating in the study. Twenty-one subjects were randomized to each of 2 groups: an aerobic training (AT) group, 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 before completion of recruitment and screening.

Study Design

Each subject underwent 2 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 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 guidelines¹² and consisted of moderate to vigorous intensity exercise on a treadmill and a cycle ergometer. Training sessions were 3 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 of warm-up, 40 minutes of 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 rate (HR) Polar Vantage Heart Watches (Adelaide, Australia). Based on the resting HR and maximal HR determined during maximal exercise treadmill testing (see below), we set training HR to 60%–75% of HR reserve based on the Karvonen formula.¹³

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 (dumbbells) exercises. We confirmed a lack of aerobic training in the NA group with a test of maximal oxygen consumption in each subject ($\dot{V}O_{2\max}$, 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, HR, and blood glucose. Electrocardiogram telemetry was also available if necessary if unusual HR or rhythms were noted.

Data Collection and Processing

Subject conditions were standardized according to established guidelines: All measures were performed after 30 minutes of supine rest; the environment was quiet and temperature controlled ($25 \pm 1^\circ\text{C}$); 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. Each subject remained in the supine position for 45 minutes before the start of data collection to reach steady state, followed by a 30-minute tilt-table test (see below).

HR was monitored continuously using a 3-lead electrocardiogram. Blood pressure was monitored using a Finometer (Finapres Medical Systems, Amsterdam, The Netherlands). The Finometer measures beat-to-beat blood pressure non-invasively using infrared plethysmography through a finger cuff. The use of the Finometer and infrared plethysmography for monitoring blood pressure changes has been well established as a noninvasive measure of beat-to-beat blood pressure¹⁴ and has been extensively validated against intra-arterial blood pressure monitoring in older adults.¹⁵ The Finometer uses waveform filtering, level correction, and an additional return-to-flow calibration to reconstruct brachial artery pressures.¹⁶

Each subject's weight was measured using a physician's balance scale. Body mass index (BMI), waist circumference, hip circumference, and hip-to-waist ratio were measured and calculated as per established guidelines.¹⁷ VO_2max was determined using a maximal Bruce treadmill protocol exercise test. The change in VO_2max was examined in all groups, including the untrained and aerobically trained subjects.

Tilt Table Testing

After being given 400 μg of sublingual GTN, each subject was placed in a 70° head-up tilt for 30 minutes. The tilt table test was considered positive if the subject demonstrated presyncopal symptoms (lightheadedness or 'dizziness') in association with at least a 30-mm Hg drop in blood pressure compared to baseline or developed outright syncope. Tilt table tolerance (TTT) was defined as the length of time on the tilt table test before the test becoming positive. We also recorded the maximal decrease in SBP (DeltaSBP), diastolic blood pressure (DBP; DeltaDBP) and the maximal decrease in mean arterial pressure (MAP; DeltaMAP) with upright tilting.

Statistical Analysis

All data analyses were done in a blinded fashion. Due to skewing of the data from the ceiling effect of 30 minutes maximum tilt time, TTT is reported as median $\pm$ standard error, whereas the remaining results are reported as mean $\pm$ standard error. Our 4 primary outcomes consisted of TTT, DeltaSBP, DeltaMAP, and change in VO_2max . A value of $P < 0.0125$ was considered significant, due to a Bonferroni correction for multiple comparisons.¹⁸ For hemodynamic changes with upright tilting, the effects of training were calculated by a 2-way analysis of variance for repeated measures (time $\times$ group). To handle the problem of right censorship of data with TTT (subjects that lasted the full 30 minutes without syncope or presyncope), a survival analysis from start of tilt was performed. This consisted initially of a Kaplan–Meier analysis, using a Mantel–Cox Log-Rank test (χ^2_{MC}) to compare the “survival curves” (with length of time on the tilt table on the x -axis) between the AT and NA groups. This was followed by Cox proportional hazards model, adjusting for the covariates of age and gender. Differences between proportions (such as the proportion of subjects with presyncopal symptoms) were handled with a Fisher exact test. Dropouts were handled on an intention-to-treat basis.¹⁸

RESULTS

Subject Characteristics

There were 2 dropouts from the study, 1 from each group. This left a total of 40 subjects (25 males and 15 females, mean age 71.6 ± 0.7 , ranging in age from 65 to 83) who completed the intervention. One dropout (AT group) was handled on an intent-to-treat basis, whereas the other (NA group) was lost to follow-up. Other than the dropouts mentioned above, all the remaining 40 subjects attended at least 90% of the training sessions. Therefore, 20 subjects from the AT group and 20 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 HR, resting blood pressure, fasting blood sugar, glycosylated hemoglobin, lipid profile, hemoglobin, hematocrit, or proportion prescribed antihypertensive medications (Table 1).

Effects of Training on Tilt Table Tolerance—Kaplan–Meier Curves

Before starting the training program, 13 in the AT group and 15 in the NA group experienced a presyncope or syncope event during upright tilting (AT vs NA group, $P = 0.366$). After the training program, 8 in the AT group and 15 in the NA group experienced presyncope and syncope. After the training program, the difference in presyncope/syncope rates was significantly different between the AT and NA groups ($P = 0.027$). The AT group demonstrated an average tilt table duration of 8.45 ± 2.30 minutes before training and an average tilt table duration of 22.29 ± 2.32 minutes posttraining. The NA group demonstrated an average tilt table duration of 7.30 ± 2.18 minutes before training and an average tilt table duration of 13.22 ± 2.07 minutes posttraining. In comparing the 2 groups, the tilt table duration was not significantly different at baseline (AT vs NA group, $P = 0.719$), but average TTT was significantly longer in the AT group after the training program (AT vs NA group, $P = 0.006$). With respect to the Kaplan–Meier curves, there was no significant difference in the survival curves before training ($\chi^2_{MC} = 1.309$, $P = 0.253$). Posttraining, TTT was significantly better in the AT group as compared with the NA group ($\chi^2_{MC} = 7.271$, $P = 0.007$, Fig. 1).

Effects of Training on Tilt Table Tolerance—Cox Proportional Hazards Model

A Cox Proportional Hazards Model was performed to adjust for the covariates of age and gender, both before starting training and after the training intervention. Before the start of the training program age ($\beta = -0.002 \pm 0.05$, $P = 0.97$), gender ($\beta = 0.011 \pm 0.39$, $P = 0.001$) and training group ($\beta = -0.59 \pm 0.38$, $P = 0.12$) were not significant coefficients in the Cox proportional hazards model with respect to TTT. After the training program was complete, neither gender ($\beta = 0.541 \pm 0.47$, $P = 0.250$) nor age ($\beta = -0.046 \pm 0.07$, $P = 0.496$) was a significant coefficient in the model. The only significant covariate posttraining for TTT was training group (AT vs NA group; $\beta = -1.25 \pm 0.47$, $P = 0.007$).

Hemodynamic Response to Upright Tilting

As shown in Table 2, there was no significant training effect on the maximal hemodynamic changes observed during upright tilting, specifically with respect to DeltaSBP ($P = 0.636$), DeltaMAP ($P = 0.302$), DeltaDBP ($P = 0.664$), and DeltaHR ($P = 0.996$).

Effects of Training on Measures of Fitness

The 3-month training program did not result in a significant increase in VO_2max (Table 3, $P = 0.027$). As shown in Table 3, there was no significant difference between the NA and AT groups with respect to training-induced changes in weight ($P = 0.640$), BMI ($P = 0.448$), waist-to-hip ratio ($P = 0.775$), or fasting blood glucose ($P = 0.020$). There was no significant difference between the 2 groups with respect to training-induced changes in SBP ($P = 0.123$), MAP ($P = 0.309$), DBP ($P = 0.231$), or resting HR ($P = 0.073$).

DISCUSSION

Aerobic training improved upright GTN tolerance in older adults with type 2 diabetes. Improvements in TTT occurred with only 3 months of aerobic training despite the fact that this was in a population at a quite high cardiovascular risk. This improvement occurred without any significant improvements in aerobic fitness, weight, BMI, waist-to-hip ratio, or blood pressure indicating that the effects of aerobic training on orthostatic tolerance may be independent of these other well-established benefits of exercise.

Previous work on the effects of aerobic exercise on orthostatic tolerance has had mixed results, demonstrating positive,⁶ negative,⁷⁻⁹ and neutral¹⁰ effects of training on the ability of subjects to withstand orthostatic stress. All investigations demonstrating either negative or neutral effects of aerobic exercise involved the examination of very intense training in young athletes ($\text{VO}_2\text{max} > 60 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)⁷⁻¹⁰ and most involved a cross-sectional design.⁸⁻¹⁰ The only study that involved both a prospective intervention and a subject population of nonathletes demonstrated a large improvement in orthostatic tolerance to upright tilting in young adult military recruits, congruent with the results of this study.⁶ To our knowledge, our study is the first to show that even older adults at very high cardiovascular risk due to type 2 diabetes, and age can improve orthostatic tolerance with regular aerobic exercise.

Potential Mechanisms

During periods of orthostatic stress, the body maintains blood flow to the brain through the arterial baroreflex, which has been shown to be insensitive in older subjects with type 2 diabetes.¹⁹ Aerobic exercise has been shown previously to improve arterial baroreflex sensitivity in both older subjects²⁰ and subjects with type 2 diabetes,⁵ congruent with the improved TTT demonstrated in our investigation. Arterial baroreceptors are located in the arterial wall,²¹ resulting in lower baroreflex sensitivity with increased vascular stiffness.²² Previous work in both middle-aged²³ and older adults²⁴ with type 2 diabetes has demonstrated a decrease in arterial stiffness with aerobic exercise, suggesting a possible mechanism for the training-induced improvement in TTT observed in this study. Alternatively, investigations in human subjects have demonstrated that aerobic exercise training reduces sympathetic tone,²⁵ which could also explain a training-related

improvement in baroreflex sensitivity.²⁶ Interestingly, the fact that we did not demonstrate a significant change in VO_2max suggests that this improvement in TTT can occur even in the absence of an improvement in overall aerobic fitness (Table 3).

Although subjects in the AT group took significantly longer to reach a level of symptomatic hypotension than those in the NA group (Fig. 1), we were unable to demonstrate a training-mediated increase in DeltaSBP, DeltaMAP, and DeltaDBP. One explanation for the lack of a training effect on the decrease in blood pressure with upright tilt is that for ethical reasons, the tilt-table test was halted if the subject demonstrated presyncopal symptoms in association with at least a 30-mm Hg drop in blood pressure (as opposed to continuing the tilt table test to outright syncope). It is also possible that a longer training intervention or larger number of subjects might have been able to detect a difference in minimum blood pressure that our study was unable to detect.

Clinical Implications

Older adults with type 2 diabetes are at increased risk of falls due to syncope, mainly due to autonomic dysfunction from their underlying illness.² This population is especially vulnerable to the adverse effects upon orthostatic tolerance of vasodilatory medications,²⁷ which also contribute to a high risk of falls in this population.²⁸ The results of our study have demonstrated that a nonpharmacological lifestyle intervention can improve orthostatic tolerance to GTN demonstrating an additional benefit of aerobic training in this population.

Limitations

Further research is needed to determine the pathophysiological mechanism for the improvement in orthostatic tolerance with aerobic exercise in our population. We also do not know if the observed improvement in TTT with aerobic exercise persisted over a longer period of time, because our subjects were only examined during the 3-month training period. Our study was also 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 4 primary outcome measures (Delta SBP, DeltaMAP, Delta DBP, TTT).

CONCLUSIONS

We demonstrated that aerobic exercise improves orthostatic tolerance while taking GTN in older adults with type 2 diabetes. This suggests that aerobic exercise should be first line therapy for orthostatic intolerance in the older adult population, even if they have been prescribed vasodilatory medications.

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FIGURE 1.

With respect to the TTT Kaplan–Meier curves, there was a significant difference in the survival curves posttraining in the AT group as compared with the NA group ($\chi^2_{MC} = 7.271$, $P = 0.007$). The y -axis represents the proportion of subjects in each group tolerating upright tilt, whereas the x -axis shows the duration of upright tilting. The tilt table test was halted if the subject demonstrated presyncopal symptoms (lightheaded-ness or ‘dizziness’) in association with at least a 30-mm Hg drop in blood pressure compared with baseline or developed outright syncope.

TABLE 1

Subject Characteristics

Measure	All Subjects	AT Subjects	NA Subjects	P
Age (yrs)	71.6 ± 0.7	71.9 ± 1.1	71.3 ± 0.9	0.471
Weight (kg)	80.3 ± 2.1	81.9 ± 2.2	79.3 ± 3.1	0.557
Height (cm)	168.5 ± 1.4	167.7 ± 2.0	169.2 ± 1.9	0.586
BMI (kg/m ²)	29.9 ± 0.7	31.2 ± 1.1	28.9 ± 1.0	0.086
Waist-to-hip ratio	0.93 ± 0.03	0.92 ± 0.05	0.94 ± 0.02	0.409
SBP (mm Hg)	144 ± 3	149 ± 6	140 ± 4	0.093
DBP (mm Hg)	82 ± 2	82 ± 3	82 ± 2	0.940
MAP (mm Hg)	103 ± 2	104 ± 3	101 ± 2	0.354
HR (bpm)	74 ± 2	73 ± 2	75 ± 2	0.574
Fasting blood glucose (mEq)	7.8 ± 0.3	7.9 ± 0.5	7.8 ± 0.4	0.808
Glycosylated hemoglobin (%)	6.7 ± 0.2	6.8 ± 0.3	6.6 ± 0.2	0.785
Total cholesterol (mmol/L)	5.0 ± 0.2	5.0 ± 0.2	5.0 ± 0.3	0.823
Low-density lipoprotein cholesterol (mmol/L)	2.7 ± 0.1	2.8 ± 0.2	2.6 ± 0.2	0.581
High-density lipoprotein cholesterol (mmol/L)	1.6 ± 0.1	1.5 ± 0.1	1.6 ± 0.1	0.755
VO ₂ max (mL·kg ⁻¹ ·min ⁻¹)	23.0 ± 1.0	21.5 ± 1.4	24.0 ± 1.4	0.236
Hemoglobin (g/L)	140 ± 2	141 ± 3	138 ± 3	0.497
Hematocrit (%)	0.420 ± 0.006	0.423 ± 0.009	0.418 ± 0.009	0.762
Antihypertensive medications				
Angiotensin-converting enzyme inhibitor	21	9	12	0.527
Diuretics	18	10	8	0.751
Alpha-1 blockers	0	0	0	1.000
Nitrates	0	0	0	1.000
Hydralazine	0	0	0	1.000
Calcium channel blockers	4	2	2	1.000
Angiotensin receptor; blockers	7	5	2	0.408
Beta-blockers	9	4	5	1.000

Demographic data for AT, NA, and all subjects are shown as mean ± standard error.

A *P* value of <0.05 was considered significant.

TABLE 2

Training and the Hemodynamic Response to Upright Tilt

Measure	AT Group Pretraining	AT Group Posttraining	NA Group Pretraining	NA Group Posttraining	P (Time × Group)
DeltaSBP	-47.9 ± 0.7	-27.7 ± 0.6	-57.8 ± 0.4	-43.0 ± 0.6	0.636
DeltaMAP	-31.8 ± 0.4	-17.7 ± 0.4	-37.4 ± 0.3	-27.0 ± 0.4	0.302
DeltaDBP	-18.3 ± 0.3	-9.3 ± 0.3	-22.3 ± 2.3	-15.3 ± 0.2	0.664
DeltaHR	+13.5 ± 1.8	+12.2 ± 1.9	+11.4 ± 1.4	+11.8 ± 1.8	0.996

The hemodynamic responses to upright tilting for AT and NA are shown as mean ± standard error.

None of these measures showed a significant effect of training effect (time × group).

TABLE 3

Responses to Training

Measure	AT Subjects	NA Subjects	<i>P</i> (Time × Group)
Weight (kg)	−0.183 ± 0.645	+0.140 ± 0.364	0.640
BMI (kg/m ²)	−0.18 ± 0.28	+0.04 ± 0.17	0.448
Waist-to-hip ratio HR	−0.003 ± 0.004	0.002 ± 0.011	0.775
SBP (mm Hg)	−12 ± 5	−2 ± 3	0.123
DBP (mm Hg)	−4 ± 2	−1 ± 2	0.231
MAP (mm Hg)	−5 ± 4	−1 ± 2	0.309
HR (bpm)	−5.2 ± 2.5	−0.3 ± 1.1	0.073
Fasting blood glucose (mEq)	−1.1 ± 0.4	−0.1 ± 0.2	0.020
VO ₂ max (mL·kg ^{−1} ·min ^{−1})	+2.7 ± 1.2	−0.6 ± 0.8	0.027

Changes in measures of fitness for AT and NA are shown as mean ± standard error.

None of the measures of fitness showed a significant training effect (time × group) due to the fact that our study was only powered to find an effect for our 3 primary outcomes.

bpm, beats per minute.