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Original article

Preliminary observations of passive exercise using whole body periodic acceleration on coronary microcirculation and glucose tolerance in patients with type 2 diabetes

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ABSTRACT

Background: The whole body periodic acceleration (WBPA) system was recently developed as a passive exercise device by providing increased pulsatile shear stress for improvement of endothelial function. This study aimed to investigate the acute effects of WBPA on coronary microcirculation and glucose tolerance in patients with type 2 diabetes (T2D).
Methods: The study subjects were 8 patients with T2D who underwent transthoracic Doppler echocardiography for the assessment of coronary flow reserve (CFR) before and immediately after a 45-min session of WBPA. The flow velocity in the distal portion of the left anterior descending coronary artery was measured at baseline and during adenosine infusion. The CFR represented the ratio of hyperemic to basal mean diastolic flow velocity.
Results: WBPA increased CFR from 2.3 ± 0.3 to 2.6 ± 0.4 ($p = 0.02$). WBPA decreased serum insulin level from 26 ± 19 μIU/ml to 19 ± 15 μIU/ml ($p = 0.01$) and increased total adiponectin from 11.6 ± 7.3 μg/ml to 12.5 ± 8.0 μg/ml ($p = 0.02$) and high molecular weight adiponectin from 4.9 ± 3.6 μg/ml to 5.3 ± 3.9 μg/ml ($p = 0.03$), whereas the serum glucose level was stable from 207 ± 66 mg/dl to 203 ± 56 mg/dl ($p = 0.8$).
Conclusions: This study demonstrates that a single session of WBPA treatment simultaneously improved coronary microcirculation and glucose tolerance in patients with T2D.
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Introduction

Exercise has been considered a cornerstone in the management of type 2 diabetes (T2D), along with diet and medications [1–4]. Patients with diabetes are advised to engage in regular moderate aerobic exercise for at least 30 min a day for at least five days a week [5]. One of the physiological changes responsible for health and cardio-metabolic benefits of exercise is mediated by changing the secretion of adipokines. Increased circulating adiponectin [6–8], particularly high molecular weight adiponectin [9,10], plays an important role in T2D due to its insulin sensitizing [6], anti-inflammatory [7], and anti-atherogenic properties [8]. However, care is sometimes needed in exercising T2D patients with complications [11]. Furthermore, the recommended intensity of exercise might not be achievable in patients with concomitant neurological and rheumatological diseases, mobility problems, and frailty among others.

Whole body periodic acceleration (WBPA) serves as an alternative or complement to active exercise because it increases shear stress to the endothelium [12]. This form of passive exercise increases the pulsatile shear stress to the endothelium and endomyocardium to increase the release of nitric oxide due to the stimulation of endothelial nitric oxide synthase (eNOS), up-regulation of eNOS, and improvement in peripheral endothelial

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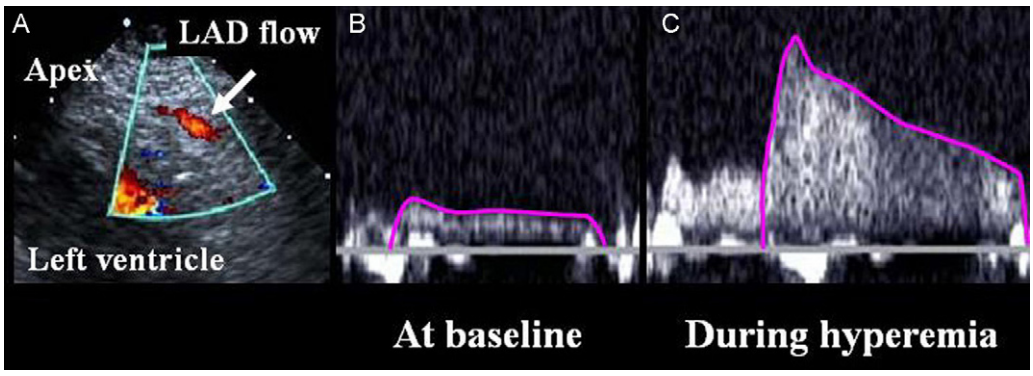

Fig. 1. Transthoracic Doppler echocardiography images demonstrating the technique of measurement of coronary flow reserve in the left anterior descending (LAD) coronary artery. (A) Visualization of coronary blood flow in the distal LAD. (B) Measurement of basal mean diastolic flow velocity. (C) Measurement of hyperemic flow velocity.

function [13–15]. Our reports showed that WBPA improved coronary microcirculation [16] and peripheral endothelial function [17], which was recently supported by experimental study [18], however, there are no studies on the effects of WBPA on glucose tolerance in humans. The present study was designed to investigate the acute effects of passive exercise with WBPA on coronary microcirculation as well as on glucose tolerance in patients with T2D. Coronary flow reserve (CFR) was measured by transthoracic Doppler echocardiography (TTDE) to assess the status of coronary microcirculation.

Methods

Study population

The study was approved by the Institutional Review Board of the Osaka Ekisaikai Hospital. The study subjects were 8 consecutive patients (8 men, 69 ± 7 years) with T2D for more than 1 year. All patients were referred for coronary angiography to evaluate coronary artery disease. We excluded patients with history of myocardial infarction, left ventricular ejection fraction of less than 40%, valvular heart disease, and dilated or hypertrophic cardiomyopathy. Patients had TTDE examination before and immediately after a session of WBPA treatment. All patients were asked to abstain from smoking and alcohol for 24 h before the study. WBPA treatment was done after >3 h of fasting. Blood samples were taken at each TTDE examination to determine plasma glucose, insulin, total adiponectin, and high molecular weight adiponectin, as previously described [19,20]. Eight patients with T2D (8 men, 69 ± 7 years) also served as an age- and gender-matched control group in order to investigate the effect of 45-min rest without WBPA treatment on glucose tolerance.

Whole body periodic acceleration

WBPA was applied using the AT-101 (Non-Invasive Monitoring Systems, Inc., Miami, FL, USA), a device that consists of a motion platform with a gurney-like appearance, driven by a two-flywheel motor assembly [16–18]. The device measures 222 cm in length, 77.5 cm in width, and 211 kg in weight. A hand-held controller allows the operator to start and stop as well as regulate the speed and acceleration of the device. With the subjects laying supine on a mattress placed on the motion platform, repetitive head-to-foot movements delivered at approximately 140 cycles/min and g of $\pm 2.2\ m/s^2$ for 45 min. A foot board strapped the patient's feet to couple the body to the motion platform during the session.

CFR measurement by TTDE

CFR was measured before and immediately after the 45 min WBPA session. For measurement of CFR, TTDE was performed with the Sequoia 512 instrument (Siemens Medical Solutions, Mountainview, CA, USA). The flow in the distal portion of the left anterior descending (LAD) coronary artery was explored with a modified foreshortened 2-chamber view. The acoustic window was around the mid-clavicular line in the fourth and fifth intercostal spaces with patients in the left lateral decubitus position, and the ultrasound beam was inclined laterally. Under the guidance of color flow mapping, the coronary blood flow in the distal LAD was identified as a color-filled tubular structure in the anterior groove area (Fig. 1A). The long-axis sections were carefully adjusted to minimize the angle between the Doppler beam and the LAD flow. Angle correction was performed if the angle between color flow and the Doppler beam was >20%. The coronary blood flow velocity was measured at baseline and after intravenous infusion of adenosine triphosphate (ATP) at a rate of 0.14 mg/kg/min for 2 min to produce hyperemia (Fig. 1B and C). The mean diastolic flow velocity was measured by tracing the contour of the spectral Doppler signal. The ratio of hyperemic to basal mean diastolic flow velocity was calculated as CFR. The values of 3 cycles were averaged for each variable in the CFR measurements. TTDE examinations were conducted by an expert sonographer with >5 years experience in echocardiography and approximately 100 CFR examinations. They were blinded to other clinical information.

Coronary angiography

Coronary angiography was performed using the standard Judkins technique. Multiple projections were used to evaluate coronary narrowing by one investigator who was blinded to the clinical data. The severity of coronary narrowing was visually estimated by comparison of the luminal diameter of the segment exhibiting narrowing to the luminal diameter of the most normal-appearing site immediately proximal to the narrowing. Significant coronary narrowing was defined if there was ≥50% diameter narrowing on coronary angiography.

Statistical analysis

Values were expressed as mean ± SD. Laboratory and echocardiographic data before and after WBPA were compared by the paired *t* test. Clinical characteristics between patients with WBPA treatment and controls were compared with chi-square statistic for categorical variables or by unpaired *t* test for continuous variables. Two-way repeated measures analysis of variance, testing for WBPA effect, ATP effect, and their interaction was used to evaluate

Table 1
Patients' characteristics.

	WBPA group	Control group	*p*-Value
Height, cm	164 ± 6	166 ± 10	0.6
Weight, kg	63 ± 8	63 ± 9	0.9
Body mass index, kg/m^2	23.5 ± 1.8	23.0 ± 2.6	0.6
Waist circumference, cm	85 ± 6	82 ± 9	0.4
Risk factor			
Hypertension, *n* (%)	7 (88)	6 (75)	0.5
Hypercholesterolemia, *n* (%)	4 (50)	3 (38)	0.6
Smoking, *n* (%)	3 (38)	3 (38)	–
History of stroke, *n* (%)	3 (38)	2 (25)	0.6
History of peripheral arterial disease, *n* (%)	1 (13)	1 (13)	–
Years since diagnosis, years	8.0 ± 5.2	7.8 ± 5.6	0.9
Coronary angiography (≥50% stenosis)			
Right coronary artery, *n* (%)	2 (25)		
LAD, *n* (%)	5 (63)		
Left circumflex coronary artery, *n* (%)	5 (63)		
Ejection fraction, %	59 ± 5	52 ± 10	0.1
Cardiac medications			
Diuretic, *n* (%)	0 (0)	2 (25)	0.1
Beta-blockers, *n* (%)	0 (0)	2 (25)	0.1
Calcium channel blockers, *n* (%)	5 (63)	2 (25)	0.1
ACE inhibitors or ARB, *n* (%)	6 (75)	4 (50)	0.3
Statin, *n* (%)	5 (63)	3 (38)	0.3
Antiplatelet agent, *n* (%)	8 (100)	6 (75)	0.1
Medications for diabetes			
Diet alone	0 (0)	0 (0)	–
Oral hypoglycemic agent	6 (75)	7 (88)	0.5
Insulin	2 (25)	1 (13)	0.5
Hemoglobin A1c, %	7.5 ± 1.2	8.2 ± 2.0	0.4
Serum creatinine, mg/dl	1.11 ± 0.28	0.97 ± 0.34	0.4
eGFR, ml min^{-1} 1.73 m^{-2}	55 ± 17	65 ± 18	0.3

Data are presented as mean value ± SD or number (%) of patients. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; LAD, left anterior descending coronary artery; and WBPA, whole body periodic acceleration.

heart rate, blood pressure, and mean diastolic flow velocity after ATP infusion in pre- and post-WBPA. Differences were considered significant at $p < 0.05$.

Results

Table 1 lists the clinical characteristics of the study participants with T2D in WBPA group and control group, respectively. All patients had significant coronary narrowing on angiography. WBPA were completed and well-tolerated in all patients, and no significant hemodynamic or mechanical complications were observed during the procedure or follow-up.

Analysis of data of all 8 patients demonstrated that CFR increased from 2.3 ± 0.3 at baseline to 2.6 ± 0.4 after a single 45-min session of WBPA ($p = 0.02$) (Fig. 2). Table 2 shows the values of hemodynamics and mean diastolic flow velocity before and after WBPA at rest and during ATP infusion. Two-way ANOVA showed no significant interactions in terms of heart rate, systolic blood pressure, and mean diastolic flow velocity.

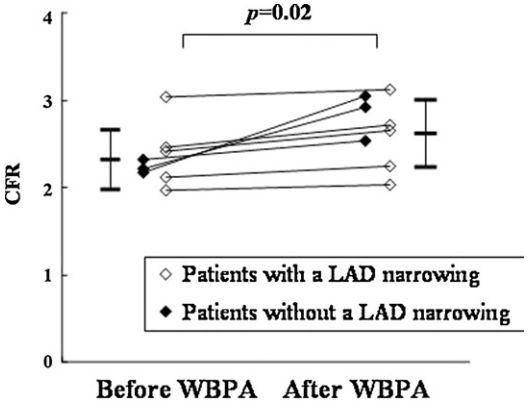

Fig. 2. Effect of whole body periodic acceleration (WBPA) on coronary flow reserve (CFR) in patients with (open square) and without (closed square) a left anterior descending artery (LAD) narrowing.

Table 2
Hemodynamics and echocardiographic results before and after WBPA.

	Before WBPA	After WBPA	*p*-Value
Heart rate, beats/min			
Baseline	66 ± 12	66 ± 9	0.7
ATP infusion	67 ± 12	68 ± 10	
Systolic blood pressure, mmHg			
Baseline	127 ± 19	141 ± 27	0.4
ATP infusion	130 ± 25	137 ± 25	
Mean diastolic flow velocity, cm/s			
Baseline	22 ± 12	21 ± 7	0.1
ATP infusion	51 ± 26*	56 ± 24*	

The column showed *p*-values for the interaction of WBPA and ATP effects, testing from two-way repeated measures ANOVA.

* $p < 0.05$ vs the corresponding parameter before ATP infusion. ATP, adenosine triphosphate and WBPA, whole body periodic acceleration.

Table 3
Laboratory data before and after WBPA.

	Before WBPA	After WBPA	*p*-Value
White blood cell, /mm^3	5926 ± 1146	4950 ± 2239	0.1
Hematocrit, %	35.3 ± 3.9	36.2 ± 3.3	0.09
High-sensitive CRP, mg/dl	0.85 ± 1.63	0.93 ± 1.77	0.1
Glucose, mg/dl	207 ± 66	203 ± 56	0.8
Serum insulin, μIU/ml	26 ± 19	19 ± 15	0.01
Total adiponectin, μg/ml	11.6 ± 7.3	12.5 ± 8.0	0.02
High molecular weight adiponectin, μg/ml	4.9 ± 3.6	5.3 ± 3.9	0.03
Urinary albumin, μg/g Cr	380 ± 850	358 ± 653	0.3

Cr, serum creatinine; CRP, C-reactive protein; and WBPA, whole body periodic acceleration.

Table 3 demonstrates the laboratory data before and after WBPA. WBPA resulted in a decrease in serum insulin concentration (26 ± 19 μIU/ml to 19 ± 15 μIU/ml, $p = 0.01$), had no significant effect on blood glucose level (207 ± 66 mg/dl to 203 ± 56 mg/dl, $p = 0.8$). In 6 patients who received oral hypoglycemic agents, serum insulin concentration decreased from 28 ± 22 μIU/ml to 20 ± 18 μIU/ml ($p = 0.02$), whereas blood glucose level was stable (214 ± 69 mg/dl to 204 ± 62 mg/dl, $p = 0.6$). Total (11.6 ± 7.3 μg/ml to 12.5 ± 8.0 μg/ml, $p = 0.02$) and high molecular weight adiponectins (4.9 ± 3.6 μg/ml to 5.3 ± 3.9 μg/ml, $p = 0.03$) increased after the treatment, respectively. WBPA had no effect on other parameters.

In the control study, 45 min of rest without WBPA treatment did not alter the serum glucose (185 ± 68 mg/dl to 177 ± 66 mg/dl, $p = 0.4$) and insulin levels (18 ± 17 μIU/ml to 18 ± 14 μIU/ml, $p = 0.7$), respectively.

Discussion

Previous observations of WBPA

Exercise training increases vascular shear stress of the peripheral and coronary endothelia, leading to a reduction in cardiovascular morbidity and mortality [1,2,5]. However, attention is needed when exercising patients with certain T2D complications, such as those with severe retinopathy (who are at risk of hemorrhage or retinal detachment), with nephropathy (at risk of proteinuria due to acute rise in blood pressure), and those with neuropathy (at risk of postural hypotension or skin infection) [11]. It is therefore important to devise alternative physical activities of moderate intensity in such T2D patients who cannot exercise at a sufficient level. Passive exercise refers to exercise performed without volitional control and is a potential alternative and complementary to active exercise. The efficacy of passive exercise as an exercise per se is, however, questionable because it does not improve hemodynamics as does active exercise [21–23].

WBPA repetitively moves the horizontally positioned body head to foot in the direction of the spinal axis. It causes inertial shifts of blood as the motion platform accelerates and decelerates to add pulses to the circulation thereby increasing shear stress to the endothelium [12]. This is one of the important benefits of exercise training because increased shear stress produces enhanced release of nitric oxide from the endothelium and endomyocardium through the activation and up-regulation of eNOS [13–15]. Our recent clinical [17] and experimental [18] investigations strongly suggest that WBPA results in improvement of endothelial function in peripheral arteries. Another study showed that CFR in response to adenosine increased after WBPA in patients with and without coronary artery narrowing [16]. Although adenosine is a vasodilator mainly in an endothelium-independent manner by rapidly increasing the local concentration of adenosine, adenosine's vasodilatory effect depends at least partly on coronary endothelial function [24–26]. To our knowledge, however, there are no data on whether the WBPA-induced modification of the blood flow in coronary and peripheral arteries and/or systemic conditions improves glucose tolerance.

WBPA on adiponectin and glucose tolerance

In the present study, we demonstrated that a single session of WBPA treatment decreases serum insulin concentration, maintaining the same level of blood glucose. This indicates that WBPA improves glucose tolerance. Correspondingly, total and high molecular weight adiponectins, which act as a key modulator of insulin sensitivity and glucose metabolism [6–10], increase after WBPA treatment. However, the acute effect of exercise on circulating adiponectin concentration is varied in the clinical setting [27,28], depending on study population and the intensity/duration of exercise. The result of the present study suggests that shear stress to the endothelium, one of the important beneficial effects of exercise, plays a central role in increasing circulating adiponectin after exercise in patients with advanced atherosclerosis. All patients included in our study had T2D for more than 1 year and concomitant coronary artery disease. Consequently, this study supports the use of WBPA in patients with T2D for improving the status of coronary microcirculation and glucose tolerance, especially in patients who are incapable or unwilling to exercise at a sufficient level.

Study limitations

Several limitations should be mentioned. The number of patients was small ($n = 8$). The degree of CFR improvement after WBPA treatment tended to be larger in patients without LAD narrowing than those with LAD narrowing ($27.0 \pm 16.0\%$ vs $6.3 \pm 3.6\%$). However, statistical analysis was not examined in this sub-analysis due to the small number of patients and inadequate statistical power. Future investigations with a large number of patients might be necessary to clarify the determinant of the degree of CFR improvement after WBPA treatment as well as to investigate the detailed mechanisms of WBPA treatment on the modifications of coronary microcirculation and adiponectin. In addition, the long-term outcome remains unknown. Furthermore, we investigated the effect of only a single 45-min session of WBPA. Repeated sessions of WBPA would strengthen the effect of WBPA, as we previously reported [18].

Most patients continued taking one or more medications during examinations, including angiotensin-converting enzyme inhibitors (75%), statins (63%), and thiazolidinedione (25%). Such medications and the degree of daily physical activity in individuals might affect the results of CFR. Also, WBPA treatment was done after >3 h of fasting. Also, glucose tolerance was unchanged in the control group. However, considering that most patients were treated with oral hypoglycemic agents, this time interval between latest fasting and WBPA treatment might not be enough to evaluate glucose tolerance.

CFR was measured by the TTDE method in the LAD only and the effect of WBPA on circulation in other coronary vessels was not evaluated due to the high success rate in obtaining adequate coronary flow velocity in the LAD than in other coronary vessels [29]. Furthermore, the TTDE method allows the measurement of coronary flow velocity without estimation of the coronary artery diameter. However, a previous study reported a close relationship in CFR measured by absolute coronary flow and flow velocity [30]. In fact, CFR derived from changes in only coronary flow velocity was used in previous large invasive studies [31,32].

Conclusions

The present study demonstrated that passive exercise using the WBPA system improved the status of coronary microcirculation and glucose tolerance in patients with T2D.

Disclosures

There is no conflict of interest and financial disclosure in our manuscript for all the authors.

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