CARDIOVASCULAR EFFECTS OF ACUTE AEROBIC PHYSICAL EXERCISE IN PATIENTS WITH DOWN SYNDROME: A PILOT STUDY

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ABSTRACT: Introduction: Individuals with Down Syndrome (DS) shows poor aerobic capacity and reduced vascular reserve, evaluated immediately after exercise. However, vascular and hemodynamic parameters and arterial stiffness indices during acute exercise have not been studied. To evaluate the effects of acute aerobic exercise on arterial stiffness, pulse wave velocity (PWV) and augmentation index (AIx@75) and to relate biochemical and vascular parameters with these indices. Method: This is a quasi-experimental study, evolving 10 individuals of both sexes with DS (21.9±8.49 years). The arterial stiffness, vascular and hemodynamic parameters were evaluated by the Mobil-O-Graph® monitor. Assessments were carried out at rest, during aerobic exercise with 50 to 60% of maximal heart rate (HRmax), and cool-down period. Results: The cardiovascular parameters evaluated during acute exercise and the cool-down period, did

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not change in relation to baseline. Heart rate increased during exercise but did not return to basal levels in the cool- down period. The AIx@75 was positively correlated with insulin (p=0.02, r=0.74) and HOMA IR values (p=0.03, r=0.71). AIx@75 was negatively correlated with pulse pressure amplification (p=0.04, r=-0.66) and positively with the reflection coefficient (p=0.01, r=0.75). PWV was positively correlated with central (p=0.02, r=0.73) and peripheral systolic blood pressure (p=0.03, r=0.67). Conclusion: This study is the first to assess vascular and hemodynamic parameters and arterial stiffness indices during aerobic acute exercise. These parameters did not change during and after exercise compared, suggesting attenuation of the vascular response. Furthermore, we demonstrate that AIx@75 was positively correlated with insulin resistance parameters.
KEYWORDS: Vascular stiffness; Pulse wave velocity; Augmentation index; Aortic pulse wave; Hemodynamic parameters.

EFEITOS CARDIOVASCULARES DO EXERCÍCIO AERÓBICO AGUDO EM PACIENTES COM SÍNDROME DE DOWN: UM ESTUDO PILOTO

RESUMO: Introdução: Indivíduos com Síndrome de Down (SD) apresentam baixa capacidade aeróbica e reserva vascular, avaliadas imediatamente após o exercício. Entretanto, parâmetros vasculares e hemodinâmicos e índices de rigidez arterial durante o exercício agudo não foram estudados. Objetivo: Avaliar os efeitos do exercício aeróbico agudo sobre a rigidez arterial, velocidade de onda de pulso (VOP) e índice de aumentação (AIx@75), relacionando-os aos parâmetros bioquímicos e vasculares. Método: Trata-se de um estudo quase experimental, envolvendo 10 indivíduos com SD de ambos os sexos (21,9±8,49 anos). A rigidez arterial, os parâmetros vasculares e hemodinâmicos foram avaliados pelo monitor Mobil-O-Graph®. As avaliações foram realizadas em repouso, durante exercício aeróbico com 50 a 60% da frequência cardíaca máxima (FCmáx) e no período de desaquecimento. Resultados: Os parâmetros cardiovasculares avaliados durante o exercício agudo e no período de desaquecimento não se alteraram em relação aos valores basais. A frequência cardíaca aumentou durante o exercício, mas não retornou aos níveis basais no período de desaquecimento. O AIx@75 correlacionou-se positivamente com os valores de insulina (p=0,02, r=0,74) e HOMA IR (p=0,03, r=0,71). O AIx@75 correlacionou-se negativamente com a amplificação da pressão de pulso (p=0,04, r=-0,66) e positivamente com o coeficiente de reflexão (p=0,01, r=0,75). A VOP correlacionou-se positivamente com a pressão arterial sistólica central (p=0,02, r=0,73) e periférica (p=0,03, r=0,67). Conclusão: Este estudo é o primeiro a avaliar parâmetros vasculares e hemodinâmicos e índices de rigidez arterial durante exercício aeróbico agudo. Esses parâmetros não se alteraram durante e após o exercício, sugerindo atenuação da resposta vascular. Além disso, demonstramos que o AIx@75 correlacionou-se positivamente com os parâmetros de resistência à insulina.
PALAVRAS-CHAVE: Rigidez vascular; Velocidade da onda de pulso; Índice de aumentação; Onda de pulso aórtica; Parâmetros hemodinâmicos.

EFECTOS CARDIOVASCULARES DEL EJERCICIO FÍSICO AERÓBICO AGUDO EN PACIENTES CON SÍNDROME DE DOWN: UN ESTUDIO PILOTO

RESUMEN: Introducción: Las personas con síndrome de Down (SD) presentan una capacidad aeróbica deficiente y una reserva vascular reducida, evaluada inmediatamente después del ejercicio. Sin embargo, no se han estudiado los parámetros vasculares y hemodinámicos ni los índices de rigidez arterial durante el ejercicio agudo. El objetivo del estudio fue evaluar los efectos del ejercicio aeróbico agudo sobre la rigidez arterial, la velocidad de la onda de pulso (VOP) y el índice de aumento (AIx@75) y relacionar los parámetros bioquímicos y vasculares con estos índices. Método: Estudio cuasiexperimental en el que participaron 10 personas de ambos sexos con SD (21,9 ± 8,49 años). La rigidez arterial, los parámetros vasculares y hemodinámicos se evaluaron mediante el monitor Mobil-O-Graph®. Las evaluaciones se realizaron en reposo, durante el ejercicio aeróbico con un 50-60 % de la frecuencia cardíaca máxima (FCmáx) y durante el período de enfriamiento. Resultados: Los parámetros cardiovasculares evaluados durante el ejercicio agudo y el período de enfriamiento no variaron con respecto al valor basal. La frecuencia cardíaca aumentó durante el ejercicio, pero no volvió a los niveles basales durante el período de enfriamiento. El AIx@75 se correlacionó positivamente con la insulina ($p = 0,02$, $r = 0,74$) y los valores de HOMA IR ($p = 0,03$, $r = 0,71$). El AIx@75 se correlacionó negativamente con la amplificación de la presión del pulso ($p = 0,04$, $r = -0,66$) y positivamente con el coeficiente de reflexión ($p = 0,01$, $r = 0,75$). La VOP se correlacionó positivamente con la presión arterial sistólica central ($p = 0,02$, $r = 0,73$) y periférica ($p = 0,03$, $r = 0,67$). Conclusión: Este estudio es el primero en evaluar los parámetros vasculares y hemodinámicos y los índices de rigidez arterial durante el ejercicio aeróbico agudo. Estos parámetros no cambiaron durante y después del ejercicio en comparación, lo que sugiere una atenuación de la respuesta vascular. Además, demostramos que el AIx@75 se correlacionó positivamente con los parámetros de resistencia a la insulina.

PALABRAS CLAVE: Rigidez vascular, velocidad de la onda de pulso, índice de aumento, onda de pulso aórtico, parámetros hemodinámicos.

1. INTRODUCTION

Down syndrome (DS) is the most common chromosomal abnormality, with a prevalence of 10.3 per 10,000 inhabitants in the United States. Mental deficiencies and delayed development vary considerably and recent decades have seen significant gains in satisfaction and quality of life in this population. In relation to other children, additional health complications increase the risk of hospitalization and may have a significant emotional and financial impact on families (Bunt; Bunt, 2014). The main diseases associated with DS are thyroid dysfunction, obesity, cardiovascular diseases and musculoskeletal alterations. The most important endocrine abnormality is thyroid dysfunction, hypothyroidism being the most prevalent (Malt *et al.*, 2013). Adults with DS shows a greater prevalence of overweight and obesity, and higher waist-

height/abdominal fat ratio (Real de Asua *et al*., 2014). Congenital heart defects may occur in 50% of this population (Irving; Chaudhari, 2012), mainly mitral valve insufficiency and prolapse in adulthood (Balli *et al*., 2016). Besides that, even without congenital and acquired heart disease, patients with DS display higher right and left ventricular performance indices than those of controls, as well as greater ventricular mass and ejection fraction (Balli *et al*., 2016). In relation to musculoskeletal changes, these individuals show a high rate of osteoporosis, low muscle tonus and reduced strength. Degenerative osteoporosis is also common in patients with DS, leading to weakness and pain (Esbensen, 2010).

A large body of evidence shows that individuals with DS display low aerobic capacity (Barnhart; Connolly, 2007; Mendonca *et al*., 2010; Wee *et al*., 2015). Wee *et al*. (2014) demonstrated that individuals with DS show lower peak oxygen uptake (VO2peak) and peak heart rate (HRpeak) (Wee *et al*., 2015). The low cardiovascular capacity in adults with DS may be secondary to lower lean muscle mass, thyroid diseases, hypotonic muscle tonus, higher incidence of obesity, or a lower sympathetic response to maximum exercise (Barnhart; Connolly, 2007). Hu *et al*. (2013) investigated arterial function after maximum exercise and observed that individuals with DS have attenuated arterial stiffness as a response to maximum exercise, when compared to their controls (Hu *et al*., 2013). Since the response to maximum exercise reflects the capacity of the vascular system to accommodate increased demand during exertion, attenuation of the vascular exchanges observed in this population suggests a decline in vascular reserve. Besides that, obesity and VO2 peak modulated this response.

In 1929, the average life expectancy of individuals with DS was 9 years, 35 years in 1982 and 55 years or older nowadays. Thereby, changes in structure and function, secondary to aging, may limit activity and restrict participation in these individuals (Barnhart; Connolly, 2007). Besides that, early aging and the different associated diseases in patients with DS favor sedentarism. The American College of Sports Medicine recommends exercise programs for individuals with DS. According to a meta-analysis that assessed the results of exercise programs for individuals with DS, the programs were effective in increasing the maximum workload, VO2peak and peak minute ventilation (Dodd; Shields, 2005). A review study by Li *et al*. (2013) assessed the impact of physical exercise on physical aptitude (balance, muscle force and strength, cardiovascular aptitude and body composition) in individuals with DS. These authors showed that light to

moderate exercise interventions improved muscle force and balance in this population (Li *et al*., 2013).

Physical activity is associated with reduced mortality from cardiovascular disease (CVD), and changes in known risk factors such as body weight, blood pressure, and serum lipids explain 59% of the beneficial effects of exercise on the most important cardiovascular outcomes. The effects of exercise on vascular parameters (endothelial function, arterial remodeling and vessel compliance) explain the 40% reduction in the remaining risk factors. In a meta-analysis study, Ashor *et al*. (2014) concluded that the effect was achieved at a higher intensity and in participants that exhibited greater arterial stiffness in basal conditions. Arterial stiffness was assessed by pulse wave velocity (PWV) and the augmentation index (AIx) (Ashor *et al*., 2014). Studies on arterial stiffness, under basal conditions, in individuals with DS are scarce. Rodrigues *et al*. (2011) demonstrated that arterial stiffness, as assessed by carotid-femoral PWV, was significantly lower in individuals with DS (7.51 ± 0.14 m/s vs. 7.84 ± 0.12 m/s; $P < 0.05$) compared to the control group (Rodrigues *et al*., 2011).

These results were confirmed by Parra *et al*. (2017) (Parra *et al*., 2017) in 51 patients with DS. Central pulse pressure (PPc) has also been considered as a measure of arterial stiffness. Hu *et al*. (2013) showed that patients with DS exhibited lower central (PPc) and peripheral pulse pressure (PPp). Although reflection time of the wave wassignificantly higher in the group with DS, AIx@75 (AIx corrected to 75% of heart rate) was similar in both groups (Hu *et al*., 2013). To the best of our knowledge, only Hu *et al*. (2013) evaluated the effect of exercise on the arterial function of individuals with DS. Assessments were conducted with subjects at rest and after 3 minutes of maximum exercise. The present study evaluated the effects of acute aerobic exercise on arterial stiffness, hemodynamic parameters, as well as central and peripheral vascular parameters in patients with DS at rest, during aerobic exercise with 50 to 60% of maximal heart rate (HRmax), and cool-down period.

2. MATERIAL AND METHODS

2.1 Participants

This is a cross-sectional study with a convenience sample. Initially, twelve subjects with DS were selected from the Association of Parents and Friends of the Disabled (APAE), and students from schools registered with the Laboratory of

Psychology and Psychosocial Intervention (LAPIP) of the Federal University of São João del Rei (UFSJ). Two subjects were excluded, one due to diagnosis of valvopathy with hemodynamic repercussion to physical exertion and the other because of discomfort and irritability during data collection.

Individuals of both sexes with DS were included in the study with clinical and cardiological authorization to perform the physical exercises. Exclusion criteria were individuals with cardiovascular disease, acute or chronic respiratory disease, smokers, and those who used non- steroid anti-inflammatory medication or vasoactive drugs.

Individuals with severe mental deficiency that precluded their execution of the proposed tests were also excluded. After initial selection and explanation of the study procedures, the parents or guardians gave their informed consent.

2.2 Assessment Protocol

Subjects initially underwent medical examination consisting of anamnesis, physical examination, electrocardiogram and biochemical examinations. Next, participants responded to the Brazilian Association of Market Research Companies' socioeconomic questionnaire (ABEP, n.d.). Subjects were then submitted to physical fitness assessment using the 1600-meter walk test, adaptation to a 4-week exercise program and evaluation of arterial stiffness and vascular and hemodynamic parameters, under basal, exercise and resting conditions.

2.3 Anthropometric data

Body mass index (BMI) was determined by the ratio between weight (kg) and height squared (kg/m²). Waist and hip circumferences were measured and the waist height (W/Ht) and waist- hip ratios (W/H) were obtained.

2.4 Echocardiographic assessment

A transthoracic echocardiographic examination was conducted using a Toshiba Medical Systems Corporation® device with participants in left lateral decubitus at rest, without sedation. The parameters assessed were right ventricular diastolic diameter (RVDD), left ventricular end- diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrial diameter (LAD), aorta diameter (AD), ejection fraction (EF) and pulmonary artery systolic pressure (PASP).

2.5 Complementary examinations

Fasting blood samples were collected between 8am and 12pm, two weeks before assessment of arterial stiffness. We analyzed lipid profile [total cholesterol, high-density lipoprotein (HDL), low density lipoprotein (LDL)], triglycerides (TG), resting glycemia, insulin, homeostasis model assessment of insulin resistance (HOMA IR) index and C-reactive protein (CRP).

2.6 Physical fitness assessment

The 1600m walk test, proposed by Almeida (2010) (Almeida *et al*., 2010), validated to calculate maximum aerobic capacity (VO2max), was conducted to assess physical fitness. The test was carried out on an 800m running track and time spent on the walk and heart rate were recorded. VO2max (l.mim-1) was calculated from the variables weight (W in kg x 2.205), age (A), sex (S, 1 for the male group and 2 for the females), time spent on the 1600m walk (T) and heart rate (HR) [VO2max = 6.952 + (0.0091 x W) – (0.0257 x A) + (0.5955 x S) – (0.2240 x T) – (0.0115x HR)]. All the participants performed the 1600m test, abstaining from other exercises, alcohol and caffeine consumption for 24 hours prior to assessment.

2.7 Physical exercise adaptation

All participants were submitted to an exercise adaptation period (twice-weekly 1-hr sessions), for four weeks, on a horizontal bicycle ergometer. The aim of the adaptation protocol was to adjust the load and determine the maximum heart rate tolerated during exertion. A cuff was used to measure blood pressure (BP) during the exercise adaptation period, as well as a heart rate monitor (Polar FT7F®), consisting of a rubber tape placed on the xiphoid appendix, and a wristwatch on the participant's right arm. Maximum heart rate was calculated by the Karvonen formula (220-age) (Karvonen *et al*., 1957), as recommended by the American College of Sports Medicine (ACSM).

2.8 Arterial stiffness assessment

The Pulse Wave Analysis Monitor (Mobil-O-Graph, IEM, Stolberg, Germany) was used to determine arterial stiffness indices, as well as vascular and hemodynamic parameters. After conventional Oscillo metric measurement of blood pressure, the cuff was inflated in the diastolic phase for 10 seconds and brachial pulse waves recorded using a high-fidelity pressure sensor. After digitization, a 3-step algorithm is applied: 1-

Brachial pressure waveforms are tested for plausibility, 2- The waves are compared for artifact recognition, 3- Next, an aortic pulse wave is generated by the ARCSolver algorithm, using a generalized transfer function. Moreover, Mobil-O-Graphy software decomposes the aortic pulse wave into an incident wave and reflection wave (Koutroumbas *et al*., 2015).

The arterial stiffness indices assessed were pulse wave velocity (PWV) and augmentation index, corrected for a heart rate of 75 bpm (AIx@75). The PWV was estimated by the mathematic model, considering several parameters in the pulse wave and wave separation analysis. The AIx@75 was defined as the difference in pressure between the peak of the reflection wave (P2) and peak of the incident wave (P1), expressed as central pulse pressure (PPc) percentage [AIx@75 = (P2-P1) / PPc x 100.

In addition to arterial stiffness indices, we assessed peripheral [systolic blood pressure (SBPp), diastolic blood pressure (DBPp), pulse pressure (PPp)], central [SBPc, DBPc, PPc, mean arterial pressure (MAP)], and hemodynamic parameters [cardiac output (CO), total vascular resistance (TVR) and cardiac index (CI) and heart rate (HR)].

Two cuffs (24-30 and 32-42 cm) were used to measure brachial artery blood pressure, according to the arm circumference of each patient (Luzardo et al., 2012). The measurements were taken at three instances: at rest, the second after three minutes of aerobic exercise on a horizontal bicycle ergometer (ErgoFit Cycle 167®) and the third after a three-minute cool-down period. Exercise initiated with zero load and velocity between 50 and 60 rotations per minute. The load was adjusted every 10 watts until reaching the target heart rate (50 to 60% of HRmax), monitored by the Polar FTF7® device.

Three consecutive measurements were taken at each stage with the equipment placed on the raised brachial artery of the left arm. The average of three acceptable measurements was considered for analysis. All the participants were instructed to maintain a postprandial state for at least three hours and abstain from exercise, consuming caffeine or stimulating foods for 24 hours.

The Mobil-O-Graph® was approved by the Food and Drug Administration (FDA) and validated for assessing peripheral and central hemodynamic and vascular parameters, according to the guidelines of the British Hypertension Society (BHS) under the European Society of Hypertension (ESH) (Franssen; Imholz, 2010; Jones *et al*., 2000). Furthermore,

the Mobil- O-Graph® was validated for assessment of the direct and indirect parameters of arterial stiffness, PWV and AIx@75, respectively (Koutroumbas *et al*., 2015).

3. RESULTS

Table 1 shows anthropometric data and biochemical examinations. Mean BMI was 27.13 ± 6.75 kg/m2, and, according to WHO criteria (2007), 40% of participants were overweight and 20% obese. With respect to central obesity, the W/H was high in 40% of the subjects (0.87 ± 0.05) and W/Ht was high in 100% of the individuals, with an average of 0.58 ±0.08 (Adelekan *et al*., 2012; McCarthy *et al*., 2006).

Table 1. Anthropometric data, biochemical examinations and maximum oxygen uptake.

Variable	Mean and SD
Age (years)	21.9 ± 8.49
Anthropometric Parameters	
Weight (Kg)	60.6 ± 17.50
Height (cm)	148.8 ± 8.24
BMI (Kg/m²)	27.13 ± 6.75
Waist circumference (cm)	85.80 ± 14.67
Hip circumference (cm)	95.10 ± 14.28
Waist Hip Ratio (W/H)	0.90 ± 0.07
Male	0.92 ± 0.07
Female	0.87 ± 0.05
Waist Height Ratio (W/Ht)	0.58 ± 0.08
Biochemical Examinations	
Red Blood Cells (M/mm^3)	4.924 ± 0.59
Hemoglobin (g/dl)	14.74 ± 1.30
Total cholesterol (mg/dl)	177.7 ± 24.50
LDL cholesterol (mg/dl)	103.5 ± 19.39
HDL cholesterol (mg/dl)	52.3 ± 11.61
Triglycerides (mg/dl)	106.4 ± 36.13
Fasting glycemia (mg/dl)	92.8 ± 6.63
Insulin (mg/dl)	10.60 ± 5.15
HOMA IR mg/dl)	2.39 ± 1.28
CRP (mg/dl)	3.07 ± 1.38
VO2max	
Female (ml/kg/min)	29.63 ±10.91
Male (ml/kg/min)	30.14± 8.46

Data are expressed in mean ± standard deviation. Abbreviations: BMI: Body Mass Index; WC: Waist circumference; HC: Hip circumference; insulin resistance index (HOMA IR). CRP: C- reactive protein; VO2max: maximum oxygen uptake.

Lipid profiles were evaluated by serum LDL, HDL and triglyceride levels showed no changes in the sample under study. Fasting glycemia and insulin levels were normal. No inflammatory changes were observed in the individuals studied, and CRP values were 3.07 ± 1.38 (mg/dl). Cardiopulmonary capacity was estimated by the 1600m walk test, VO2max was 29.63 ± 10.91 (ml/kg/min) for women and 30.14 ± 8.46 (ml/kg/min) for men. According to the Brazilian Cardiorespiratory Fitness Classification Based on

Maximum Oxygen Consumption, (Pucci *et al*., 2016) considering the age and sex, very weak cardiopulmonary aptitude was observed in the entire sample.

Interatrial communication (IAC), present in 40% of study participants, did not exhibit hemodynamic repercussion in any of the subjects.

Vascular (peripheral and central blood pressures) and hemodynamic parameters, and arterial stiffness indices are represented in Table 2. Except for HR, no significant differences were found between rest (basal), aerobic exercise and cool-down periods for the parameters assessed. Heart rate increased significantly during exercise and did not return to basal levels after exercise. The test was interrupted for one participant who exhibited discomfort, irritability and asked to abandon the assessment procedure.

Table 2. Blood pressure (peripheral and central), hemodynamic and arterial stiffness parameters at during rest, exercise and cool-down phases

Variable	Rest	Exercise	Cool-down	p-value
Peripheral pressure				
SBPp (mmHg)	113.4 ± 9.94	118.2 ± 8.62	114.5 ± 16.0	0.4474
DBPp (mmHg)	69.53 ± 9.41	74.07 ± 7.42	70.0 ± 9.43	0.0606
MAPp (mmHg)	89.6 ± 8.36	93.87 ± 7.36	90.6 ± 11.5	0.2019
PPp(mmHg)	43.83 ± 9.76	46.10 ± 9.48	44.13 ±10.8	0.8436
Central Arterial Pressure				
SBPc (mmHg)	101.4 ± 8.82	104.4 ± 8.24	102.2 ±14.53	0.6024
DBPc (mmHg)	71.0 ± 9.35	75.8 ± 7.55	71.97 ± 9.4	0.0604
PPc (mmHg)	30.37 ± 7.62	28.67 ± 3.66	30.2 ±9.0	0.7882
PPA	1.49 ± 0.12	1.55 ± 0.11	1.49 ± 0.12	0.0781
Hemodynamic				
Systolic Volume (ml)	59.4 ± 11.12	55.42 ± 8.1	55.72 ±10.35	0.2782
Cardiac output (l/min)	4.5 ± 0.42	4.78 ± 0.55	4.63 ± 0.68	0.2555
TVR (s*mmHg/ml)	1.20 ± 0.10	1.19 ± 0.13	1.18 ± 0.09	0.9504
Cardiac index (l/min*1/m²)	2.95 ± 0.56	3.13 ± 0.59	2.90 ± 0.46	0.2151
Heart rate (bpm)	77.17 ± 9.95	87.24 ±12.21*	83.1 ± 9.83	0.0401
Arterial Stiffness				
Augmentation pre (mmHg)	6.56 ± 3.69	5.36 ± 2.27	6.16 ± 2.74	0.5603
AIx@75 (%)	21.13 ± 11.3	24.10 ± 9.57	24.0 ±8.59	0.3212
PWV (m/s)	4.89 ± 0.34	5.06 ± 0.51	4.86 ±0.56	0.3729

Data are represented as mean ± SD. With a p-value <0.005. Abbreviations: SBPp – Peripheral systolic blood pressure; DBPp – Peripheral diastolic blood pressure; MAP – Mean arterial pressure; PPp – Peripheral pulse pressure; SBPc – Central systolic blood pressure; DBPc – Central diastolic blood pressure; PPc – Central pulse pressure; PPA – Pulse pressure amplification; TVR – Total vascular resistance; HR – Heart rate; AIx@75 – Augmentation index corrected to 75% of heart rate; PWV – Wave pulse velocity. * p<0.05 in relation to rest.

Table 3 shows the correlations between arterial stiffness indices (AIx@75 and PWV) and anthropometric data, biochemical examinations and VO2max. AIx@75 was positively correlated with insulin and HOMA IR values. By contrast, PWV did not correlate with any of the variables assessed.

Table 3. Correlation between arterial stiffness parameters and anthropometric data, biological examinations and maximum oxygen uptake

Variable	AIx@75 (%)		PWV (m/sec)	
	p- value	r- value	p- value	r- value
Age	0.73	0.12	0.11	0.53
BMI (Kg/m²)	0.56	0.21	0.39	0.31
W/H (cm)	0.84	-0.07	0.72	0.13
W/Ht (cm)	0.87	0.06	0.64	0.17
LDL cholesterol (mg/dl)	0.59	-0.19	0.84	0.07
Triglycerides (mg/dl)	0.62	0.18	0.52	0.23
Fasting glycemia (mg/dl)	0.24	-0.4	0.11	-0.54
Insulin (mg/dl)	**0.02**	0.74	0.42	-0.28
HOMA IR (mg/dl)	**0.03**	0.71	0.38	-0.3
CRP (mg/dl)	0.41	-0.29	0.85	0.07
VO2max-female (ml/kg/	0.17	-0.64	0.84	0.15
VO2max-male (ml/kg/mi	0.12	-0.7	0.13	0.69

Data are represented with a p-value <0.05. Abbreviations: BMI: Body Mass Index; WC: Waist circumference; HC: Hip circumference; CRP: C-reactive protein; VO2max: Maximum oxygen intake.

The correlation between arterial stiffness (AIx@75 and PWV) and peripheral and central vascular pressures and hemodynamic parameters is depicted in Table 4. AIx@75 was negatively correlated with PPA, SV and CO and positively with the reflection coefficient (Figure 1). The PWV was positively correlated with SBPp, MBPp and SBPc (Figure 2).

Table 4. Correlation between arterial stiffness indices, and vascular and hemodynamic parameters.

Variable	AIx@75 p- value	AIx@75 r- value	PWV m/s value	PWV m/ value
Peripheral				
Arterial Pressure				
SBPp (mmHg)	0.66	-0.66	**0.03**	0.67
DBPp (mmHg)	0.11	-0.53	0.15	0.49
MBPp (mmHg)	0.17	-0.47	**0.03**	0.67
PPp (mmHg)	0.49	0.25	0.9	0.05
HR (bpm/min)			0.9	-0.06
Central Arterial Pressure				
PPA	**0.04**	-0.66	0.8	-0.09
SBPc (mmHg)	0.58	-0.2	**0.02**	0.73
DBPc (mmHg)	0.12	-0.53	0.13	0.51
PPc (mmHg)			0.87	0.06
Hemodynamic				
Systolic Volume (ml)	**0.01**	-0.87	0.6	0.19
CO (l/min)	**0.04**	-0.66	0.45	0.27
TVR (s*mmHg/ml)	0.97	-0.01	0.57	-0.19
CI (l/min*1/m²)	0.56	-0.21	0.54	-0.22
Arterial Stiffness				
Augmentation Pressure (mmHg)			0.61	0.18
Reflection Coefficient	0.01	0.75	0.64	0.17
PWV (m/s)	0.87	0.06		

Data are represented with a p-value <0.005. Abbreviations: SBPp – Peripheral systolic blood pressure; DBPp – Peripheral diastolic blood pressure; MBP – Mean blood pressure; PPp – Peripheral pulse pressure; HR – Heart rate; PPA – Pulse pressure amplification; SBPc – Central systolic blood pressure; DBPc –

Central diastolic blood pressure; PPc – Central pulse pressure; CO – Cardiac output; TVR – Total vascular resistance; CI: Cardiac index; AIx@75 – Augmentation index corrected to 75% of heart rate; PWV – Pulse wave velocity.

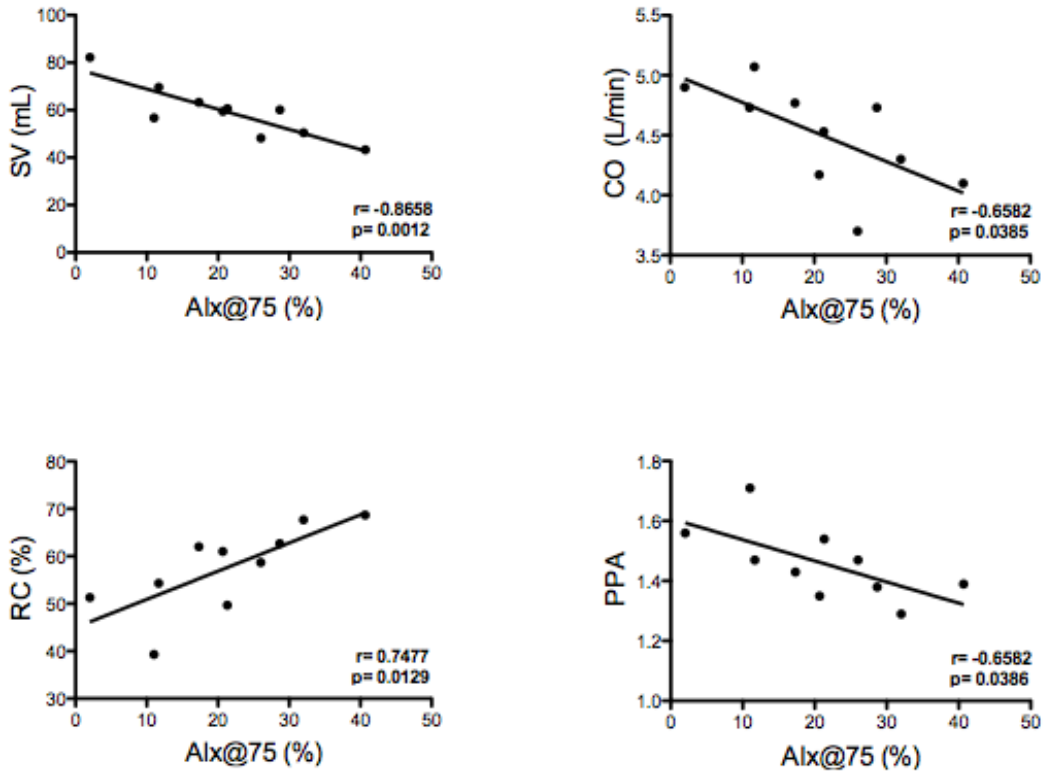

Figure 1. Correlation between augmentation index (AIx@75) and systolic volume (SV), cardiac output (CO), reflection coefficient (RC), and pulse pressure amplification (PPA) at rest.

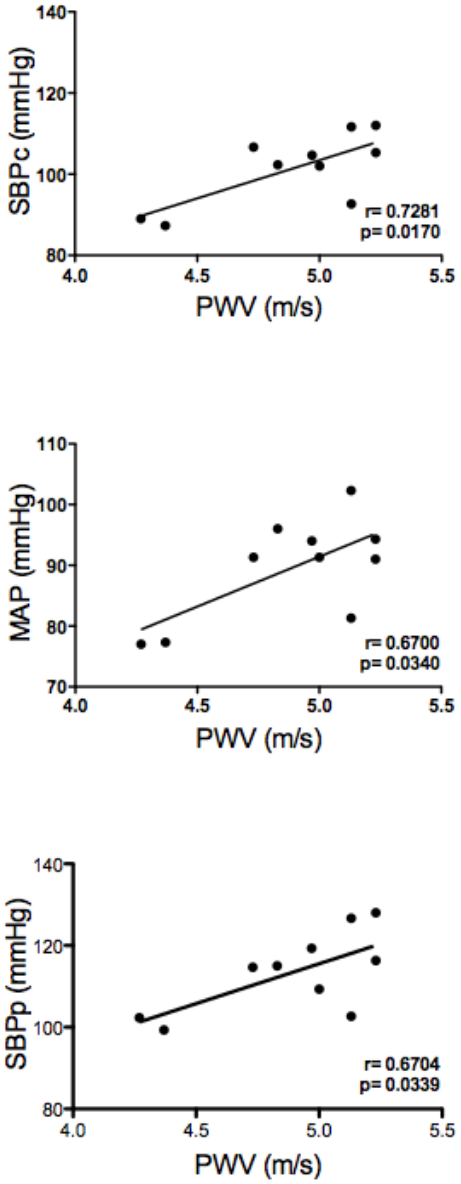

Figure 2. Correlation between pulse wave velocity (PWV) and central diastolic blood pressure (DBPc), peripheral mean arterial pressure (MAP) and peripheral systolic arterial pressure (SBPp).

Left atrial (29.2±3.765 mm), aorta (26±3.859 mm), right ventricular (RVDD=22.1±4.748X mm) and left ventricular (LVEDD= 38.1±4,533 mm and LVESD=23.1±4.095 mm) diameters, as well as EF (70.1±6.367%) and PASP (21.7±3.561mmHg) were in the normal range. Arterial stiffness, AIx@75 and PWV did not correlate with the echocardiographic parameters (Data not shown). According to ABEP, 70% of the sample was classified as socioeconomic classes b1 and b2, with monthly family income between ≈US$1.470 and $2.804 and 30% as socioeconomic classes c1 and c2, with monthly family income between ≈US$492 and $820.

4. DISCUSSION

The present study demonstrated that the vascular and hemodynamic parameters and arterial stiffness indices evaluated during acute exercise and in the cool-down, period did not change in relation to the basal level. Heart rate increased significantly during exercise but did not return to basal levels in the cool-down period. The AIx@75 was positively correlated with insulin and HOMA IR values. In relation to cardiovascular parameters, AIx@75 was negatively correlated with PPA, SD and CO and positively with the reflection coefficient. PWV was positively correlated with SBPp, MBPp and SBPc.

Many Coort studies have sought to quantify the effect of exercise on cardiovascular mortality and all causes of death in general. Changes in known CVD risk factors (reduced weight, blood pressure and lipid levels) explain a large part of the beneficial effects of exercise on cardiovascular outcomes (Polisseni; Ribeiro, 2014).

Besides these factors, the exercise modality (aerobic, resistance and combined) can also modulate a VOP and AIx. These authors observed that aerobic exercise significantly improved PWV and AIx. The present study assessed the effects of acute aerobic exercise on arterial stiffness, PWV and AIx@75.

The responses to acute exercise may provide important clinical and physiological information (Yan *et al*., 2014). The parameters evaluated during exercise and at rest did not differ from basal values, suggesting an inadequate response to physical exercise. Part of this inadequate response may be due to the reduced aerobic capacity of participants, evidenced by the low heart rate achieved during exertion (50 to 60% of HRmax). Hu *et al*. (2013) were the first to assess arterial stiffness using AIx@75, before and after maximum exercise and found that the response to exercise of patients with DS was attenuated in relation to the control group, suggesting a decrease in vascular reserve in this population (Hu *et al*., 2013). Immediately after exercise, arterial stiffness increases as a response to a rise in blood pressure. Physical exercise activates the sympathetic nervous system and vascular function is partially regulated by autonomic modulation. Earlier studies provide indirect evidence that patients with DS exhibit autonomic dysfunction during exercise (Fernhall; Otterstetter, 2003), as well as a decline in the release of epinephrine (Fernhall *et al*., 2009).

The HR reached during exercise was 50 to 60% of HRmax. This was a significant increase from basal level and remained elevated in the cool-down period. This result suggests a delay in autonomic recovery resulting from greater sympathetic predominance

or delayed vagal withdrawal (Sun *et al*., 2016). Wee *et al*. (2014) observed that patients with DS exhibited attenuated VO2peak and HRpeak, regardless of obesity or age (Wee *et al*., 2015).

Insulin resistance was assessed by serum HOMA IR and insulin levels. Real Asua *et al*. (2014) and Parra *et al*. (2014) verified high levels of these markers in individuals with DS, a finding not confirmed in the present study (Real de Asua *et al*., 2014).

Arterial stiffness and insulin resistance are correlated with morbidity and mortality. In a Chinese population-based study without diabetic participants, Fu *et al*. (2017) showed that carotid- femoral PWV (cpPWV) was positively correlated with HOMA-IR. In the present study, we are the first to show that AIx@75 and not PWV was positively correlated with insulin and HOMA IR, suggesting a relationship between reflection wave magnitude and insulin resistance in DS patients (Fu *et al*., 2017).

In the present study, AIx@75 was negatively correlated with PPA. Pulse pressure amplification, defined as the relationship between the distal (brachial artery) and proximal pulse pressure (aorta artery), is inversely related to arterial stiffness, organ damage and mortality (Breet *et al*., 2017). In healthy subjects, PPA increases between the aorta and brachial arteries, due, in part, to the progressive rise in arterial stiffness in the vascular system and change in reflection wave. These results confirm, in patients with DS, what has been observed in healthy individuals, namely, an inverse relationship between AIx@75 and PPA.

AIx@75 exhibited a strong positive correlation with the reflection coefficient. This index is calculated by the ratio between peak reflection wave and incident wave pressures, after left ventricle contraction. The magnitude of the reflection angle depends on arterial stiffness (Westerhof; Westerhof, 2012).

In the present study, PWV (4.89 ± 0.34 m/s) was lower than the values reported by Rodrigues *et al*. (2011) (Rodrigues *et al*., 2011). These authors were pioneers in analyzing carotid-femoral PWV in individuals with DS and observed that PWV was significantly lower in the DS group (7.51 ± 0.14 m/s) when compared to the controls (7.84 ± 0.12 m/s). This difference cannot be explained by the factors that most influence PWV (age and height). The age (21.9 ± 8.49 years) and height (148.8 ± 8.24 cm) of the participants of the present investigation were similar to those of a study by Rodrigues *et al*. (2011) (21.0 ± 1.0 years and 147.0 ± 1.0 cm). This difference may be related to the method applied to assess PWV. In the present study, we used Mobil-O- Graphy, which

calculates PWV employing a mathematical model from oscillometric pressure generated in the brachial artery. By contrast, Rodrigues *et al*. (2011) assessed PWV using pressure transducers placed on the common carotid and femoral artery. These authors also found that the difference in PWV between the DS and control groups disappeared when PWV was normalized by SBPp, suggesting that chronic hypotension in this population may contribute to preserving vascular function.

In the present study, PWV was positively correlated with SBPp, MBPp and SBPc. A similar result was obtained by Rodrigues *et al*. (2011). These authors observed that PWV correlated with SBPp. This relationship is expected because PWV is affected by blood pressure at the time of measurement.

Studies on healthy adults show a decline in PWV after maximum exercise, likely due to the vasodilator response to exercise (Bunsawat *et al*., 2017; Melo *et al*., 2016). In the present study, PWV did not change significantly during acute exercise or in the cool-down period in relation to baseline. This different result may be attributed to the low heart rate achieved by the participants (50 to 60% of HRmax).

In a meta-analysis study, Li *et al*. (2017) assessed the impact of overweight and obesity on the arterial stiffness of individuals without hypertension, diabetes or cardiovascular disease (Li *et al*., 2017). Overweight and obese individuals displayed a significantly higher carotid-femoral PWV and AIx than the controls, even in the absence of risk factors for cardiovascular diseases. Patients with DS show a high prevalence of overweight and obesity (Soler Marín and Xandri Graupera, 2011). In our study, 40% of participants were overweight and 20% obese, as assessed by BMI. Despite the high prevalence of overweight and obesity in patients with DS, AIx@75 and PWV did not correlate with BMI. Given that BMI is unable to differentiate lean mass from fat mass and is limited to identifying differences in adiposity related to age, sex and ethnicity (Jackson *et al*., 2002), we also assessed W/Ht and W/H. The W/H is considered an important risk factor for developing cardiovascular diseases (Lam *et al*., 2015; Savva *et al*., 2013), as is the W/Ht. Since individuals with DS exhibit short stature, the W/Ht has been used to estimate central obesity in this population (Real de Asua *et al*., 2014). Real de Asua *et al*. (2014) demonstrated that 90% of individuals with DS had high W/Ht indices. Similar to the studies of Real de Asua *et al*. (2014), 100% of the sample in the present study exhibited high W/Ht indices, according to established parameters (Fu *et al*.,

2017; Parra *et al*., 2017). Unexpectedly, AIx@75 and PWV also did not correlate with these indices. This result may be partially attributed to the small sample size.

Dyslipidemia is strongly associated with the increased risk of cardiovascular disease in the general population (Thongtang *et al*., 2022). Children with DS display a less favorable lipid profile than controls, even after adjusting for weight (Adelekan *et al*., 2012). Zamorano *et al*. (1991) showed that TG, TC, LDL-C levels are higher and HDL-C lower in children with DS when compared to controls (Zamorano *et al*., 1991). By contrast, Real de Asua *et al*. (2014) found no difference in lipid profile in 51 patients with DS compared to controls. In the present study, the lipid profile of patients was also within normal limits. No correlation was found between AIx@75 and PWV and lipid levels in the sample under study.

Several congenital anomalies may be associated with DS. In a sample of 467 patients with DS, heart anomaly was the most common, present in 44% of the sample (Stoll *et al*., 2015). In the present study it was found that 40% of the patients exhibited interatrial communication (IAC). This finding reinforces the results of Bermudez *et al*. (2015), who found 42.1% with atrial septal defect, 15.1% with atrioventricular septal defect and 14.6% with atrial septal and ventricular septal defect in a sample of 604 patients (Bermudez *et al*., 2015).

This study exhibits a number of limitations. The first is the small number of participants, which is not representative of the target population. The second was the poor physical conditioning of the patients, precluding assessment of vascular and hemodynamic parameters and arterial stiffness indices during and after reaching submaximal heart rate. Despite these limitations, the present study was the first to assess vascular and hemodynamic parameters and arterial stiffness during acute aerobic exercise.

5. CONCLUSION

This study is the first to evaluate the vascular and hemodynamic parameters and arterial stiffness indices during acute aerobic exercise. These parameters did not change during and after exercise in relation to the basal period, suggesting an attenuated vascular response. Moreover, we are the first to demonstrate that AIx@75 correlates positively with the parameters of insulin resistance. The low aerobic capacity was demonstrated by the low values of VO2max and by the attenuated HRmax reached during the effort. These

results suggest that the use of conventional protocols for the evaluation of HRmax for individuals with DS, are not adequate and new studies with protocols specific to this population are necessary.

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Brisa D'Louar Costa Maia: Select the patients, conceptualization, investigation, data curation, statistical analysis, writing and editing the original draft.

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Claudia Marotta Neves: Contributed to the cardiovascular data collection and reviewed the manuscript for important intellectual content.

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Tatiellem Conceição Moraes: Contributed to the data collection.

Cristiano Andrade Quintão Coelho Rocha: Contributed to the data collection.

Gleisy Kelly Neves Gonçalves: Critically reviewed the manuscript for important intellectual content.

Maria Glória Rodrigues-Machado: Conceptualization, formal analysis, statistical analysis, investigation, methodological supporting, project administration, supervision, validation, and revision of the original draft.

All authors read and approved the final manuscript.

All participants signed and informed consent form.