Family History of Hypertension is Associated with Anthropometric and Nitric Oxide Bioavailability Alterations in Adolescents

José Fernando Oliveira¹, Michel Kendy Souza¹, Rodrigo Vanerson Passos Neves¹, Geiziane Leite Rodrigues Melo¹, Brande Ranter Alves Soares, Luiz Humberto Rodrigues Souza¹,², Ioranny Raquel Castro Sousa¹, Rafael Reis Olher¹, Thiago Santos Rosa¹, Nanci Maria França¹, Milton Rocha Moraes¹

¹Graduate Program on Physical Education, Catholic University of Brasilia, Distrito Federal, Brazil; ²University of Bahia, Bahia, Brazil

ABSTRACT

Oliveira JF, Souza MK, Melo GLR, Soares BRA, Neves RVP, Souza LHR, Sousa IRC, Olher RR, Rosa TS, França NM, Moraes MR. Family History of Hypertension is Associated with Anthropometric and Nitric Oxide Bioavailability Alterations in Adolescents. JEPonline 2016; 19(5):38-48. Systemic arterial hypertension (SAH) is a serious global health problem. Aside from the adult population, hypertension also affects the adolescent population, given the existence of a genetic predisposition and certain biopsychosocial changes associated with its development. Few studies have analyzed and associated the combination of family history, physical activity, anthropometric profile and fitness in blood pressure reactivity and bioavailability of nitric oxide in adolescents undergoing Shuttle run and cold-press tests. We evaluated 172 adolescents (N = 60♂; N = 112♀), which were classified as children of normotensive parents (CN; N = 38♂; N = 48♀) and children with a parental history of hypertension (CH; N = 22♂; N = 64♀). The subjects were divided into active and sedentary. The findings indicate the importance of analyzing family history predictors of hypertension, such as the anthropometric and biochemical changes that often precede the development of cardiovascular disease in adolescents. Children with a parental history of hypertension showed higher body fat, higher nitrite levels at rest and decreased bioavailability of salivary nitric oxide after an exercise test.

Key Words: Hypertension, Physical Fitness, Heredity, Young
INTRODUCTION

Systemic arterial hypertension (SAH) is characterized as a multifactorial disease associated with genetics, advanced age, metabolic conditions, and hormonal changes that are linked to cardiovascular diseases and other complications (30). Obesity, in particular, is a major factor in the development of SAH (especially in the children population) (13,32). Hence, there is a major need to propose strategies aimed at understanding the multifactorial genesis of SAH in children and adolescents to help establish control measures and prevention of cardiovascular disease.

Among the various etiological factors that can cause SAH, the three most commonly cited are a genetic trait (4,27), an increase in body fat, and a low level of physical fitness (12,44). With respect to the importance of genes, it is increasingly apparent that within the genome are genetic determinants that influence blood pressure (5). For certain, there is the heritable component of blood pressure that helps in predicting the likelihood of developing SAH (15), especially in children and adolescents (5).

While the renin-angiotensin-aldosterone system (RAAS) is implicated in cardiovascular disease and the predisposition to essential hypertension (2), as is true with either dysfunction in the production or the bioavailability of NO indicates endothelial dysfunction (24), genetic studies are too expensive and time consuming (42). Thus, less expensive and easy to use instruments are important tools in public health research. In this sense, the family history (FH) is the axis of history in various clinical areas (1,18), and it has a strong correlation with the candidate genes for SAH. This is especially the case when the history of cardiovascular disease is identified in the children of hypertensive parents (5). Hence, in this regards, family history is very helpful and a less expensive means to determining the risks of cardiovascular and metabolic diseases (40).

Moreover, Lo et al. (22) point out that increased body weight and low energy consumption are also important risk factors for the development of SAH. The excess body fat and physical inactivity increase the levels of factors involved in the RAAS, the increase oxidative stress, and increase in inflammatory condition (38); capable of inducing endothelial dysfunction that results in an increase in blood pressure (17).

Although many studies analyze SAH predictors alone (23,31), the purpose of this study was to examine the influence of family history of hypertension and the level of physical activity as predictors of SAH (including anthropometric, physical fitness, blood pressure reactivity, and bioavailability of NO due to different stimuli). Our hypothesis is that children of hypertensive parents (CH) show changes related to the anthropometric profile, physical fitness, salivary concentrations of nitrite and pressor reactivity when compared with the children of normotensive parents (CN).

METHODS

Subjects
This study was conducted in accordance with the Declaration of Helsinki (Resolution 196/96 of the National Health Council). All subjects (parents or legal guardians of the volunteer) signed a consent form that explained the research objectives and risks with experimental
procedures. Parents performed a medical history to characterize the historical SAH in first grade and the use of antihypertensive medications. This history allowed for classifying the two groups of teenagers who were referred to as CH and CN. We evaluated 172 adolescents (N = 60♂; N = 112♀), divided in CN (control group, N = 38♂; N = 48♀) and CH (experimental group, N = 22♂; N = 64♀). After classification of the groups, the questionnaire was conducted on physical activity level (IPAQ) in the adolescents. It identified them as active and sedentary, subdivided into CN assets (N = 41; ♂ N = 24, ♀ N = 17), sedentary CN (N = 45; ♂ N = 14, ♀ N = 31), CH assets (N = 49; ♂ N = 12, ♀ N = 37), sedentary CH (N = 37; ♂ n = 10, ♀ N = 27). All subjects were students of a technical high school in the State of São Paulo, Brazil, with ages ranging from 14 to 18 yrs (16.02 ± 0.94 yrs). The study was approved by the Ethics Committee of the Catholic University of Brasilia (No. 1.093.260).

Procedures
After these procedures was initiated, we collected the anthropometric measurements, BP, BP hyper-reactivity, cardiorespiratory fitness, and maximal isometric handgrip force. Saliva samples were collected for salivary nitrite analysis. Table 1 presents the experimental design.

<table>
<thead>
<tr>
<th>First Day</th>
<th>Second Day</th>
<th>Third Day</th>
<th>Fourth Day</th>
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</thead>
<tbody>
<tr>
<td>IPAQ</td>
<td>Resting BP</td>
<td>Resting BP</td>
<td>Handgrip Test</td>
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<td>Antropometric</td>
<td>Baseline Salivar NO</td>
<td>Baseline Salivar NO</td>
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<td></td>
<td>Shuttle Run</td>
<td>Cold Pressor Test</td>
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<td></td>
<td>Post-Test BP</td>
<td>Post-Test BP</td>
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<tr>
<td></td>
<td>Post-Test Salivar NO</td>
<td>Post-Test Salivar NO</td>
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</tr>
</tbody>
</table>

IPAQ = International Physical Activity Questionnaire, BP = Blood Pressure, NO = Nitric Oxide

Anthropometrics Measurements
Stature, body mass, and waist/neck circumference were measured to calculate body mass index (BMI) and waist-to-height ratio (WHtR). Fat percentage was determined with a skinfold compass (Lange®, USA), as previously described by Slaughter et al. (36). Triceps and calf skinfolds were collected in triplicate and mean value was used to calculate body composition.

Cardiovascular Parameters
Heart rate (HR) and BP were measured at rest, after 10 min seated, and after the cold pressor test, 20 m shuttle-run test, and handgrip test. The data were obtained using an automated noninvasive BP monitor (3AC1-1PC, Microlife, Widnau, Switzerland). Rest BP was classified for adolescents up to 17 yrs old by gender and height percentile (10), for adolescents with 18 yrs old the VI Brazilian Guideline of Arterial Hypertension was applied (37). Systolic (SBP) and diastolic (DBP) values and HR were used to calculate the subjects’ rate pressure product (RPP) and pulse pressure (PP).

Cold Pressor Test
The protocol for the Cold Pressor Test (CPT) was adapted from a previous study (16) in which the subjects place their right hand in the water (4 °C), up to the wrist for 1 min (3,39). Blood pressure was measured at the beginning and at the end of the test. The subjects with
an increase in SBP of ≥25 mmHg or ≥20 mmHg for DBP were classified as hyper-reactive. Values under this parameters were considered normal (43).

**Cardiorespiratory Test**
To evaluate the subjects’ cardiorespiratory capacity, the 20 m shuttle-run test (20 m SR) test was used to estimate the VO\(_2\) max (21).

**Salivary Nitrite**
Salivary samples were collected before and immediately after CPT and 20 m SR. The subjects were asked to move the cotton in the mouth back and forth until it was soggy, which was then placed in a Falcon tube and, immediately, frozen until the end of the collection. After, saliva was centrifuged and supernatants were stored at –20 °C in 1.5 mL Eppendorf\(^\circ\) tubes (Cral, SP, Brazil) for nitrite analyses. The Griess reaction was used to determine nitrite concentrations. Briefly, N-(1-naphthyl)-ethylenediamine (NED) (Sigma\(^\circ\), USA) was prepared at 0.1% and sulfanilamide (Sigma\(^\circ\), USA) at 1%, both with phosphoric acid at 2.5% as a diluent. Saliva (50 μL) and the Griess reagent (50 μL) were mixed and placed in microplates. Absorbance was measured at 570 nm in a VersaMax Tunable (Molecular Devices, USA), and sodium nitrite (NaNO\(_2\)) was used as standard (14). The data were analyzed by Microplate software 6.0 (BIO-RAD Laboratories Inc, USA).

**Handgrip Test**
To determine the maximal voluntary contraction (MVC) three trials were performed using a handgrip dynamometer (Jamar Hydraulic Hand Dynamometer 5030 J1, Patterson Medical, Bolingbrook, IL, USA). Each trial was separated by 1 min. The subject was seated in a chair without supporting the back and arms in a backrest and armrest, respectively. With the dominant hand, the handle remained neutral (thumb up) as the subject pressed with the fingers for 4 sec (34). The highest value was determined as the MVC. To guarantee objectivity, the same researcher performed all tests. Blood pressure and HR were measured before, immediately after the last trial, and 5 min later.

**Statistical Analyses**
We used the orthogonal contrast for comparisons between the 4 groups, as well as confirmation of the differences by the F test with Tukey post hoc (sedentary CH, active CH, sedentary CN, active CN). To compare the combined groups, active vs. sedentary and normotensive vs. hypertensive, we used the Student \(t\) test. The significance level was set at 5%. The data were analyzed using the Statistical Package for the Social Sciences Software (SPSS, v.22, Chicago, IL).

**RESULTS**
Variables that showed differences between variances (F test, P<0.05) were ΣSkinfold (mm), Waist-to-Height ratio, fat percentage (%), HR (beats·min\(^{-1}\)), salivary nitrite (μM) Delta salivary Nitrite at SRTest (μM), maximal oxygen consumption (mL·kg\(^{-1}\)·min\(^{-1}\)), father and mother’s BMI. The differences between groups are indicated in Table 2. The variable PP (mmHg) showed a significant difference between CN vs. CH (P<0.05).
Table 2. Mean, Standard Error and P-Values between the Four Groups Evaluated.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Children of Normotensive Sedentary</th>
<th>Children of Normotensive Active</th>
<th>Children of Hypertensive Sedentary</th>
<th>Children of Hypertensive Active</th>
<th>Contrast to Four Groups</th>
<th>P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Active vs. Sedentary</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)</td>
<td>22.86(3.12)</td>
<td>22.28(2.77)</td>
<td>23.62(3.63)</td>
<td>23.01(3.12)</td>
<td>0.3147</td>
<td>0.220</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>46.17(7.27)</td>
<td>47.62(6.89)</td>
<td>45.59(7.47)</td>
<td>46.82(7.26)</td>
<td>0.6278</td>
<td>0.227</td>
</tr>
<tr>
<td>ΔSkinfold (mm)</td>
<td>32.10(5.19)</td>
<td>29.55(5.16)</td>
<td>33.68(6.85)</td>
<td>31.58(5.90)</td>
<td>0.0185</td>
<td>0.009</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>71.65(6.20)</td>
<td>70.79(4.14)</td>
<td>73.08(6.07)</td>
<td>72.22(5.60)</td>
<td>0.3194</td>
<td>0.314</td>
</tr>
<tr>
<td>WHtR</td>
<td>0.44(0.44)</td>
<td>0.43(0.02)</td>
<td>0.45(0.04)</td>
<td>0.44(0.03)</td>
<td>0.0037</td>
<td>0.015</td>
</tr>
<tr>
<td>FAT (%)</td>
<td>24.68(3.46)</td>
<td>22.82(3.57)</td>
<td>25.65(4.18)</td>
<td>24.37(3.60)</td>
<td>0.0088</td>
<td>0.006</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>115.81(8.90)</td>
<td>117.54(10.43)</td>
<td>115.71(11.37)</td>
<td>115.44(10.58)</td>
<td>0.7783</td>
<td>0.646</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72.32(7.74)</td>
<td>70.73(5.58)</td>
<td>73.16(6.97)</td>
<td>72.73(6.09)</td>
<td>0.3799</td>
<td>0.322</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>86.82(6.80)</td>
<td>86.34(6.50)</td>
<td>87.35(8.11)</td>
<td>86.96(6.99)</td>
<td>0.9381</td>
<td>0.691</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>43.50(9.49)</td>
<td>46.81(8.17)</td>
<td>42.55(6.13)</td>
<td>42.71(7.67)</td>
<td>0.0615</td>
<td>0.163</td>
</tr>
<tr>
<td>HR (beats·min⁻¹)</td>
<td>86.19(6.43)</td>
<td>82.00(6.94)a</td>
<td>83.91(5.43)b</td>
<td>82.17(6.37)c</td>
<td>0.0066</td>
<td>0.002</td>
</tr>
<tr>
<td>RPP/100</td>
<td>99.91(11.61)</td>
<td>96.35(11.50)</td>
<td>97.19(12.47)</td>
<td>94.94(12.03)</td>
<td>0.2358</td>
<td>0.113</td>
</tr>
<tr>
<td>Delta SBP CPT</td>
<td>11.64(11.93)</td>
<td>13.85(15.44)</td>
<td>12.59(10.90)</td>
<td>12.92(9.68)</td>
<td>0.8653</td>
<td>0.495</td>
</tr>
<tr>
<td>Delta DBP CPT</td>
<td>7.80(8.57)</td>
<td>7.46(11.71)</td>
<td>9.73(10.54)</td>
<td>6.37(7.75)</td>
<td>0.4581</td>
<td>0.212</td>
</tr>
<tr>
<td>NO (µM)</td>
<td>300.71(5.96)</td>
<td>300.15(8.33)</td>
<td>324.08(33.34)</td>
<td>323.34(39.02)c</td>
<td>&lt;0.000</td>
<td>0.855</td>
</tr>
<tr>
<td>Delta NO (µM)</td>
<td>18.53(17.06)</td>
<td>14.77(21.33)</td>
<td>-21.82(30.74)</td>
<td>-22.16(30.14)</td>
<td>&lt;0.000</td>
<td>0.599</td>
</tr>
<tr>
<td>VO₂ max (mL·kg⁻¹·min⁻¹)</td>
<td>36.33(3.89)</td>
<td>41.57(6.02)a</td>
<td>36.78(4.00)b</td>
<td>38.85(4.79)b</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HandGrip (kgf)</td>
<td>30.71(7.67)</td>
<td>35.24(9.04)</td>
<td>33.68(9.99)</td>
<td>33.02(10.11)</td>
<td>0.1517</td>
<td>0.173</td>
</tr>
<tr>
<td>Father BMI (kg·m⁻²)</td>
<td>25.81(2.26)</td>
<td>26.67(3.46)</td>
<td>28.05(2.91)a</td>
<td>27.52(2.62)</td>
<td>0.0020</td>
<td>0.704</td>
</tr>
<tr>
<td>Mother BMI (kg·m⁻²)</td>
<td>24.43(2.64)</td>
<td>25.13(2.68)</td>
<td>27.79(3.61)</td>
<td>27.14(2.52)</td>
<td>&lt;0.0001</td>
<td>0.955</td>
</tr>
</tbody>
</table>

aP<0.05 vs. Children of Normotensive Parents Sedentary; bP<0.05 vs. Children of Normotensive Parents Active; cP<0.05 vs. Children of Hypertensive Parents Sedentary. Abbreviations: BMI = Body mass index; LBM = lean body mass; ΔSkinfold = sum of triceps and calf skinfolds; WC = waist circumference; WHtR = waist-to-height ratio; FAT (%) = fat percentage; SBP = systolic BP; DBP = diastolic BP; MAP = mean arterial pressure; PP = pulse pressure; HR = heart rate; RPP = rate pressure product; Delta SBP CPT = Delta SBP in Cold Pressor Test; Delta DBP CPT = Delta DBP in Cold Pressor Test; NO = Salivary nitrite; Delta NO = Delta salivary nitrite in Shuttle-run 20 meters; VO₂ max = maximum oxygen consumption
The findings of this study indicate that: (a) family history of hypertension is associated with a higher percentage of body fat, sum of skinfolds and waist-to-height ratio (visceral fat) in sedentary hypertensive teens; (b) children with a family history of hypertension (CH) have a higher concentration of salivary nitrite at rest relative to children of normotensive (CN); (c) after an incremental exercise test to exhaustion showed a decrease in salivary nitrite levels in the children with a family history of hypertension (CH), the children with a family history of no hypertension (CN) showed an increase in salivary nitrite; and (d) sedentary CH parents have higher body mass index in comparison the CN parents.

The assessment of family history is a fundamental tool in the practice of clinical medicine (1,18). It shows globally the impact that genetics, environment, and shared behavior have on the individual (5,40). Camci et al. (5) found an increase in the prevalence of deletion allele (D allele) polymorphism of the angiotensin converting enzyme (ACE) in normotensive children with a positive pressure in the first FH (36.2%) and second grade (38.3%). In our study, while the sedentary adolescents with a family history of hypertension did not show abnormal BP values, they did show a higher percentage of body fat and higher waist-to-height ratio (Table 2).

Ponsonby et al. (29) report that the D allele polymorphism of ACE, as well as being associated with SAH, is also correlation with an increase in body fat and waist circumference in children and adolescents. Thus, it is possible to infer that adolescents with a family history of hypertension present changes in adiposity that increase the importance of anthropometric measurements as predictors of hypertension in school age children. Although the resting blood pressure and the blood pressure after the CPT test were not different between groups, the NO concentration was higher in the CH teenagers at home. Increased body fat (particularly visceral fat) can generate an inflammatory condition capable of inducing an increased NO release in children with obesity that can be regarded as a risk marker (8). This would explain the increase in NO in the sedentary CH subjects who was overweight.

Interestingly, though, NO levels were also elevated in the active CH, which showed lower fat percentage. This would indicate that body composition is not the only parameter able to interfere with the mechanisms that modulate the bioavailability of NO. There is also the possibility that in stages that precede the significant increase in BP (in the youth) the body increase the levels of NO in order to maintain the set point pressure, and that during the aging process there would be a decrease of this counter-regulation (7).

The CH had decreased NO levels after exercise, most studies with normotensive and hypertensive subjects report increased bioavailability of NO after exercise sessions with constant or incremental load (6,28,33), such as what occurred with the CN in the present study. This greater bioavailability of NO occurs in response to shear stress, which stimulates the activity of the endothelial (i.e., NO synthase enzyme). In this context, oxidative stress may be an important mechanism to explain the conflicting results of the delta variation of NO after exercise in the CH group. The increased production of free radicals produced during exercise in subjects with a lower antioxidant capacity may infer scavenging of NO, decreasing its bioavailability (28). In this regards, to our understanding, there are knowledge no studies that have evaluated the levels of NO after an exercise session in adolescents, especially in
teenagers of a family history of hypertension or genetic changes relative to hemodynamic control.

It is worth noting that genetic factors are only part of the predictors of SAH, since behavioral and environmental factors (e.g., diet and physical activity) also contribute to its development (5,10,13). In this context, we analyzed the BMI of the parents of the subjects in our study as a sensitive indicator to their energy balance. Our results showed that parents and hypertensive mothers have higher BMI. Parents with greater adiposity reveal a cross-talk between adipogenic and hypertensive mechanisms (19,25) that points to bad eating habits in the family that can directly influence the children’s body composition (25).

On the other hand, the results indicate that a higher level of physical activity (even among the parents with a higher BMI) helped to prevent the anticipated increase in adiposity among the teens of the CH group. In addition, active adolescents had lower resting HR and increased $\text{VO}_2\text{max}$. Both physiologic responses are commonly associated with a better status (35,41). Therefore, parents should encourage their children to increase the level of physical activity in to prevent cardiometabolic diseases and nullify the negative effects of bad eating habits of people who are part of the teenager’s network (20). Also, as pointed out by Foschini et al. (11), regular exercise promotes the reduction of body fat in obese adolescents with DD genotype for ACE.

Our findings indicate that the level of physical activity appears to interfere only with the $\text{VO}_2\text{max}$ of adolescents. It did not have a negative effect on the subjects’ handgrip strength. It is likely that because of the hormonal factors that relate to aging, muscular strength does not appear to depend on the level of physical activity (26) or the physical activities in this age group (9).

**Limitation of the Study**

One limitation is the absence of gene analysis associated with SAH. However, it is clear that the use of family history is an inexpensive and easy tool to use for many professionals (1,18). Thus, it is important to assess the nutritional status of subjects, especially in future studies to aggregate information related to body composition.

**CONCLUSIONS**

The findings in the present study indicate the importance of analyzing family history predictors of hypertension, particularly the anthropometric and biochemical changes that may precede the development of cardiovascular disease in adolescents. Children with a parental history of hypertension showed higher body fat, higher nitrite levels at rest and decreased bioavailability of salivary nitric oxide after an exercise test. This strengthens the need for the assessment of physical fitness, family anamnesis, and hemodynamic factors in screening in-school adolescents, as adjuvant treatment to preventing the development of cardiometabolic diseases. This can be done through practical exercise medicine methods (i.e., increasing the level of physical activity) to help mitigate the risk factors linked to genetic inheritance or environmental changes (e.g., physical inactivity and a sedentary lifestyle).
REFERENCES


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