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Factors associated with arterial stiffness in children aged 9-10 years

Fatores associados ao aumento da rigidez arterial em crianças de 9 e 10 anos

ABSTRACT

OBJECTIVE: To analyze the factors associated with stiffness of the great arteries in prepubertal children.

METHODS: This study with convenience sample of 231 schoolchildren aged 9-10 years enrolled in public and private schools in Vitória, ES, Southeastern Brazil, in 2010-2011. Anthropometric and hemodynamic data, blood pressure, and pulse wave velocity in the carotid-femoral segment were obtained. Data on current and previous health conditions were obtained by questionnaire and notes on the child's health card. Multiple linear regression was applied to identify the partial and total contribution of the factors in determining the pulse wave velocity values.

RESULTS: Among the students, 50.2% were female and 55.4% were 10 years old. Among those classified in the last tertile of pulse wave velocity, 60.0% were overweight, with higher mean blood pressure, waist circumference, and waist-to-height ratio. Birth weight was not associated with pulse wave velocity. After multiple linear regression analysis, body mass index (BMI) and diastolic blood pressure remained in the model.

CONCLUSIONS: BMI was the most important factor in determining arterial stiffness in children aged 9-10 years.

DESCRIPTORS: Child. Pulse Wave Analysis. Blood Flow Velocity. Vascular Stiffness. Risk Factors. Overweight.

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RESUMO

OBJETIVO: Analisar fatores associados à rigidez arterial dos grandes vasos arteriais em crianças pré-púberes.

MÉTODOS: Estudo com amostra de conveniência de 231 escolares de nove e 10 anos de idade matriculados em instituições públicas e privadas de Vitória, ES, 2010-2011. Foram obtidos dados antropométricos e hemodinâmicos, pressão arterial e velocidade de onda de pulso no segmento carotídeo-femoral. Dados sobre condições de saúde atuais e pregressas das crianças foram obtidas por meio de questionário e anotações no cartão de saúde da criança. Foi aplicada regressão linear múltipla para identificar a contribuição parcial e total dos fatores na determinação dos valores da velocidade de onda de pulso.

RESULTADOS: Dentre os escolares, 50,2% eram meninas e 55,4% tinham 10 anos de idade. Entre as classificadas no último tercil de velocidade de onda de pulso, 60,0% apresentavam excesso de peso, maiores médias de pressão arterial, circunferência da cintura e relação cintura/estatura. O peso ao nascer não foi associado à velocidade de onda de pulso. Após análise de regressão linear múltipla, permaneceram no modelo as variáveis índice de massa corporal e pressão arterial diastólica.

CONCLUSÕES: Excesso de peso foi o mais importante fator na determinação da rigidez arterial de crianças.

DESCRITORES: Criança. Análise de Onda de Pulso. Velocidade do Fluxo Sanguíneo. Rigidez Vascular. Fatores de Risco. Sobre peso.

INTRODUCTION

Traditional cardiovascular risk factors and associated alterations can act for decades, even before the onset of clinical manifestations of cardiovascular events.^{11,22} Arterial stiffness, an important determinant of blood pressure (BP) elevation and a predictor of adverse cardiovascular events,^{10,17} can manifest as early as in childhood – in children with low levels of physical activity, type 1 diabetes, or obesity.^{3,4,6}

The stiffness of the great arteries can be determined by various methods; the most indicated is measurement of pulse wave velocity (PWV), as it is easy to obtain and has good reproducibility.²⁴ Carotid-femoral PWV has become the most widely used method for assessing the degree of stiffness of the great arteries.

Epidemiological studies have observed an increased incidence of hypertension in children, probably due to its association with overweight and physical inactivity.^{7,13} Considering the association between arterial stiffness and hypertension, the evaluation of arterial stiffness in children²⁴ can clarify this association at an early age. Age, sex, body mass index (BMI), and BP are important factors in determining arterial stiffness from childhood. Li et al⁸ (2004) and Donald et al⁴ (2010) stated that systolic BP (SBP) in childhood was

positively associated with arterial stiffness. Donald et al⁴ (2010) and Aatola et al¹ (2010) observed that age was positively associated with PWV. According to Núñez et al¹⁴ (2010), obese children had higher PWV than their normal-weight peers. The same was observed in the study by Sakuragi et al¹⁹ (2009), where BMI and percentage of body fat were associated with higher carotid-femoral PWV levels in children and adolescents.

In recent years, special attention has been given to the assessment of these risk factors from a life cycle perspective. This approach was based on studies that evaluated the association of birth weight and the development of chronic diseases, confirmed by subsequent studies in different countries. This evidence led to the development of the hypothesis of fetal origins of disease, known as the Barker hypothesis,^{2,15} which proposes that exposures during critical development periods (pregnancy and early childhood) may lead to permanent metabolic and/or structural changes to ensure the survival of the fetus in adverse conditions; however, these adaptations may increase the risk of developing chronic diseases in adulthood.

The relationship between low birth weight and arterial stiffness remains controversial, especially in low- and

middle-income countries, as few studies have assessed this relationship in children from these regions; most studies were conducted in adults. Therefore, it is difficult to determine the exact moment at which the alterations found in the arteries were produced or whether these are typical of hypertension. Studies in children may contribute to a better understanding of this process in countries such as Brazil.

This study aimed to analyze the factors associated with stiffness of the great arteries in prepubertal children.

METHODS

This study had a convenience sample of 231 children aged 9-10 years enrolled in public and private schools in Vitória, ES, Southeastern Brazil, who had already participated in a previous study.⁵

The sample size was calculated to reject the null hypothesis, with type I error of 5.0%, statistical power of 90.0%, and minimum difference in PWV of 0.5 m/s between groups. Consequently, the sample needed to comprise 224 children. Families were invited to participate in the study, considering the child's prior participation in other studies. Data were collected from July 2010 to November 2011 at the Health Sciences Center of the Universidade Federal do Espírito Santo (UFES), using questionnaires and clinical examinations.

In the initial assessment, 250 children aged 9-10 years came to the Cardiovascular Research Clinic (CRC) to be examined. Of these, 19 were excluded for not undergoing the main tests involved in this study (PWV and BP). The sample consisted of 231 children, of whom 50.2% were girls and 55.4% were 10 years old.

The examinations were performed by trained researchers in a calm, quiet, and climate-controlled environment (22°C-24°C). The children made a scheduled visit to the CRC and fasted (10h-14h) before undergoing the blood tests; their BP was measured using the oscillometric method with an automatic device (OMRON® HEM-705CP), and their PWV was measured. The children were seated in comfortable chairs, and chair height was adjusted so that their feet were flat on the floor. The measurements were made on the left arm, which was supported by a movable stand that maintained the brachial artery at heart level. Cuffs appropriately sized to fit the children's arms were used; to choose the correct size, arm circumference was measured at the midpoint between the acromion and olecranon processes. The OMRON® child cuff was used for subjects with arm circumference 16-22 cm and the OMRON® adult cuff for subjects

with arm circumference 23-33 cm. Three BP measurements were obtained, with a two-min interval between them. SBP, diastolic BP (DBP), and heart rate (HR) were determined by the arithmetic mean of the last two measurements. SBP and DBP were classified as normal ($\leq 90^{\text{th}}$ percentile for age and sex), borderline (90^{th} - 95^{th} percentile) or high ($\geq 95^{\text{th}}$ percentile), as recommended by the VI Brazilian Guidelines on Arterial Hypertension.²¹ Later, they were re-categorized as normal BP ($< 95^{\text{th}}$ percentile) or high BP ($\geq 95^{\text{th}}$ percentile).

PWV was obtained after resting in the supine position for five minutes, and the subjects wore clothing that allowed easy access to the right femoral and carotid pulses. A tape measure was used to measure the distance between the sternal manubrium and the femoral pulse. PWV was measured by the simultaneous capture of pulse waves in the right carotid and femoral arteries. Dedicated software (Complior; Artech Medicale, France) assessed the adequacy of pulse waves; for positive cases, PWV was calculated by the ratio between the manubrium-femoral distance and the time delay between the two pulses. The PWV of every child was determined based on the mean, which was calculated automatically from 12 heartbeats at a regular HR. It was classified into tertiles based on the following cut-off points: tertile 1, < 5.1 m/s; tertile 2, 5.1 - 5.5 m/s; and tertile 3 > 5.5 m/s.

Anthropometric data were collected as recommended by the World Health Organization (WHO).²⁴ Body weight was measured on an electronic scale (Toledo®, model 2096; Brazil) with precision of 100 g. Height was measured by a portable stadiometer (Seca®, model 206) attached to a flat wall with no baseboard.^a BMI was calculated, and the child was classified as normal weight or overweight according to WHO criteria. Waist circumference (WC) was measured using an anthropometric tape (Sanny®) at the midpoint between the lower edge of the lowest rib and the iliac crest. The waist-to-height ratio (W/H) was obtained from the ratio of the waist and height measurements. The assessment of pubertal stage was performed using the criteria proposed by Tanner²³ (1962), and was reported by the children. Data on birth conditions, eating habits, and the child's current health, as well as the durable consumer goods available at home were obtained through interviews with one of the parents or guardian.

Socioeconomic status was classified based on ownership of consumer goods and education level of the head of the household, as recommended by the Brazilian Association of Research Companies, and grouped into

^a World Health Organization. Indicators for assessing infant and young child feeding practices. Conclusions of consensus meeting held 6-8 November 2007 in Washington D.C., USA, 2007. Washington (DC); 2007.

three categories: A+B, C, D+E.^b This variable was only used for sample characterization.

Birth weight was recorded based on the information on the child's health card. Approximately 30.0% of the cards did not include this data. In such cases, this was reported by the mother. Additionally, information on whether the delivery was preterm was collected.

The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. Student's t-test for independent samples and the Mann-Whitney test were used to compare the means of continuous variables with normal distribution and non-parametric variables, respectively. The Chi-squared test (X^2) or Fisher's exact test were used to compare proportions. One-way analysis of variance (ANOVA), followed by a Tukey test, were used to compare more than two means. The Kruskal-Wallis test was used for non-parametric variables. Pearson's and Spearman's correlation coefficients were used to test the correlations of the variables, according to their distribution. A multiple linear regression was used to identify the partial and total contribution of the factors in determining PWV values. To be included in the linear regression model, the variables with non-normal distribution were log-transformed. The residues of linear regression were evaluated for normality. The significance level was set at $\alpha < 0.05$.

Statistical analyses were performed using SPSS for Windows, version 18.0.

This study was approved by the Research Ethics Committee of the Health Sciences Center of the Universidade Federal do Espírito Santo (Case 144/2010). The children's participation was voluntary, and their families signed an informed consent form.

RESULTS

The main clinical characteristics of the participants were stratified according to the PWV tertile, with a mean of 5.3 m/s (standard deviation 0.52 m/s), minimum value of 4.1 m/s, and maximum of 7.8 m/s (Table 1). The only factor associated with PWV was nutritional status; 39.0% of the children classified in the highest PWV tertile were overweight, while this ratio was 33.0% ($p = 0.01$) in the lower tertiles.

Height was the only variable that was not associated with PWV (Table 2). Mean SBP and DBP increased from the first to the third PWV tertile ($p < 0.01$). The same occurred with the anthropometric variables WC, W/H, and body weight ($p = 0.01$; Table 2). The differences between tertiles were due almost exclusively to the increases in BP and in the variables related to the

excess weight of the children in the third tertile, when compared with the first two.

Birth weight was not associated with PWV ($p = 0.68$). The higher the child's BMI, the greater the PWV: 40.0% of the children with BMI > 20.3 kg/m² were in the highest PWV tertile ($p = 0.01$; Table 3).

Anthropometric variables and BP were significantly correlated with PWV (Table 4). However, due to collinearity between some of the anthropometric variables tested, only BMI and W/H were included in the multiple regression model. The other variables in the model were SBP, DBP, and sex.

Residual analysis demonstrated homoscedasticity. The factors that explained the changes in PWV were BMI and DBP ($p < 0.01$; Table 5).

DISCUSSION

BMI was associated with PWV in children aged 9-10 years. Although other anthropometric variables were also associated, only BMI remained in the final regression model. This finding is similar to that of Sakuragi et al¹⁹ (2009), Núñez et al¹⁴ (2010), and Celik et al³ (2011), in which a positive association was observed between overweight and arterial stiffness in children and adolescents. Although obesity is an important risk factor for cardiovascular disease, the pathophysiological mechanisms that associate it with arterial stiffness are not fully understood,¹⁸ especially in the age group assessed in the present study.

Unlike other studies, no significant association was observed between birth weight and PWV. The relationship between birth weight and arterial stiffness remains controversial. Martin et al⁹ (2000) found a negative correlation between birth weight and carotid artery stiffness, assessed by ultrasound. Miles et al¹² (2011) found no association between arterial stiffness and birth weight, as assessed by carotid-femoral PWV. Conversely, in the assessment of carotid-femoral PWV in adolescents, Salvi et al²⁰ (2012) found a negative association between low birth weight and PWV. However, birth data was obtained directly from clinical records, thus reducing the chance of recall bias.

Studies assessing arterial stiffness in children are controversial. This is mainly due to the divergent methodologies used to measure arterial stiffness, such as different devices and arterial segments assessed. The distribution of blood components varies depending on the location of the vessel. The central arteries have a higher degree of elasticity because of high elastin/collagen ratio and low influence of smooth muscle tone. In contrast, the

^b Associação Brasileira de Empresas de Pesquisa. Critério de classificação econômica Brasil. São Paulo; 2011 [cited 2010 Oct 15]. Available from: <http://www.abep.org/novo/Content.aspx?ContentID=139>

Table 1. Distribution of sociodemographic, anthropometric, sex, blood pressure, and birth conditions variables, stratified by pulse wave velocity tertiles. Vitória, ES, Southeastern Brazil, 2010-2011.

Variable	Pulse wave velocity (m/s)						p	Total	
	< 5.1		5.1 a 5.5		> 5.5			n	%
	n	%	n	%	n	%			
Sex							0.16		
Masculine	37	33.0	38	34.0	37	33.0		112	50.0
Feminine	50	45.0	35	31.0	27	24.0		112	50.0
Socioeconomic class							0.56		
A+B	44	39.0	33	29.0	36	32.0		113	52.0
C+D	39	37.0	37	36.0	28	27.0		104	48.0
Nutritional status							0.01		
Normal weight	54	44.0	45	36.0	25	20.0		124	56.0
Overweight	33	33.0	28	28.0	38	39.0		99	44.0
Systolic blood pressure*							0.44		
Normal	85	39.0	71	33.0	60	28.0		216	96.0
High	2	25.0	2	25.0	4	50.0		8	4.0
Diastolic blood pressure*							0.88		
Normal	84	38.0	71	33.0	63	29.0		218	97.0
High	3	50.0	2	33.0	1	17.0		6	3.0
Birth weight							0.59		
Normal	74	38.0	64	33.0	58	29.0		196	87.0
Low	13	47.0	9	32.0	6	41.0		28	13.0
Preterm							0.97		
Yes	9	40.0	7	30.0	7	30.0		23	10.0
No	78	39.0	65	33.0	57	28.0		200	90.0

* Fisher's exact test.

Table 2. Means and standard deviations of the hemodynamic and anthropometric variables, stratified by pulse wave velocity tertiles. Vitória, ES, Southeastern Brazil, 2010-2011.

Variable	Pulse wave velocity tertile (m/s)									p
	< 5.1			5.1 a 5.5			> 5.5			
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
SBP (mm/Hg) ^a	87	103	9	73	103	9	64	108 ^c	9	< 0.01
DBP (mm/Hg) ^a	87	62	7	73	63	8	64	66 ^c	7	< 0.01
Weight (kg) ^a	87	35.1	7.6	73	37.3	9.7	64	41.5 ^c	11	< 0.01
Height (cm) ^a	87	140	7	73	141	7	64	142	7	0.18
	n	Median	P ₂₅ ;P ₇₅	n	Median	P ₂₅ ;P ₇₅	n	Median	P ₂₅ ;P ₇₅	
WC (cm) ^b	87	60.8	55.7;67.2	72	60.6	56;73.2	63	66.3 ^c	59.1;75.6	< 0.01
W/H (cm) ^b	87	0.43	0.41;0.49	72	0.43	0.39;0.51	63	0.48 ^c	0.42;0.53	< 0.01
BMI (kg/m ²) ^b	87	17.2	15.5;19.9	73	17.6	15.4;22.1	64	20.2 ^c	16.9;23.3	< 0.01

SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; W/H: waist-to-height ratio; BMI: body mass index

^a ANOVA for parametric variables.^b Kruskal-Wallis test for nonparametric variables.^c Statistically significant according to Tukey's test.

Table 3. Birth weight, blood pressure, and nutritional status, stratified by pulse wave velocity tertiles. Vitória, ES, Southeastern Brazil, 2010-2011.

Variable	Pulse wave velocity (m/s)						p	Total	
	< 5.1		5.1-5.5		> 5.5			n	%
	n	%	n	%	n	%			
Birth weight (kg)							0.68		
≤ 2,999	33	43.0	24	32.0	19	25.0		76	34.0
3,000 to 3,499	28	35.0	29	37.0	22	28.0		79	35.0
≥ 3,500	26	38.0	20	29.0	23	33.0		69	31.0
SBP (mmHg)							0.19		
≤ 100	35	44.0	28	36.0	16	20.0		79	35.0
101 to 107	31	41.0	21	28.0	23	31.0		75	33.0
≥ 108	21	30.0	24	34.0	25	36.0		70	31.0
DBP (mmHg)							0.01		
≤ 59	39	50.0	24	31.0	15	19.0		78	35.0
60 to 65	32	43.0	25	34.0	17	23.0		74	33.0
≥ 66	16	22.0	24	33.0	32	45.0		72	32.0
BMI (kg/m ²)							0.01		
≤ 16.4	33	44.0	29	38.0	14	18.0		76	34.0
16.4 to 20.2	36	48.0	18	24.0	21	28.0		75	34.0
≥ 20.3	18	25.0	26	35.0	29	40.0		73	33.0

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index

Table 4. Simple correlation between pulse wave velocity and anthropometric variables, birth weight, and breastfeeding duration. Vitória, ES, Southeastern Brazil, 2010-2011.

Variable	Pulse wave velocity (m/s)	
	r	p
SBP ^a (mmHg)	0.19	< 0.01
DBP ^a (mmHg)	0.22	< 0.01
WC ^b (cm)	0.19	< 0.01
W/H ^b (cm)	0.18	< 0.01
Weight ^a (kg)	0.24	< 0.01
Height ^a (cm)	0.08	0.23
BMI ^b (kg/m ²)	0.20	< 0.01
Birth weight ^a (g)	0.08	0.24

SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; W/H: waist-to-height ratio; BMI: body mass index

^a Pearson's correlation.

^b Spearman's correlation.

peripheral vessels have less elasticity, as they have a lower elastin/collagen ratio. Thus, the measurement method and the arterial segment evaluated must be considered. The results will probably not be the same if measurements are done in different segments. The values obtained in the aortic-brachial segment will

be higher than those obtained in the carotid-femoral, considering the amount of elastin in each segment.²⁴ This study used the carotid-femoral PWV because it is considered to be the best method for assessing stiffness of the great arteries, especially the aorta.

The high frequency of overweight was probably related to the sample selection strategy. The participants had already participated in previous studies. Therefore, it is possible that parents who were more concerned with their child's weight responded more favorably to the invitation to participate in this study. This bias, however, does not hinder the objectives of this study, which did not aim to estimate the prevalence of structural or functional alterations in children, but rather to associate these variables with an outcome that characterizes stiffness of the great arteries, the carotid-femoral PWV.

Another limitation of this study is its cross-sectional design, which is not suitable for inferring causal association. Cohort studies provide the best conditions for assessing findings.^{20,26} However, the measurements were checked for quality control and the appropriate methodology was used for establishing the associations found in this study.

This is one of the first studies in Brazil to assess arterial stiffness measured by carotid-femoral PWV in prepubertal children. The results of the present study can

Table 5. Multiple linear regression* for the dependent variable pulse wave velocity. Vitória, ES, Southeastern Brazil, 2010-2011.

Explanatory variables	Estimated coefficient	Standard error	t	Beta	P
Constant	4.047	0.317	12.763		< 0.01
BMI (kg/m ²)	0.028	0.010	2.684	0.197	< 0.01
DBP (mm/Hg)	0.012	0.005	2.321	0.157	0.02

BMI: body mass index; DBP: diastolic blood pressure

* Adjusted for systolic blood pressure, diastolic blood pressure, and sex.

contribute to a better understanding of this subject in different locations where the lifestyle differs from that of the countries in which these parameters are usually studied. Arterial stiffness is often measured in adults, but its use in children has been previously reported. Most studies have demonstrated an association between increased PWV, age, and BP.¹⁶ In this study, BP was controlled in the linear regression adjustment to assess PWV, and the age range studied was narrow (9-10 years). Thus, it did not affect the PWV result of in the studied population or the other findings.

Although BP was measured three times under controlled environmental conditions by a trained professional, this measurement cannot be considered as a reflection of the

BP of the assessed children. Ideally, measurements are carried out at different times. Nonetheless, children who were in puberty were excluded, thus avoiding potential hormonal effects on the outcome (PWV) and on related factors such as overweight.

Overweight was the most important factor in determining arterial stiffness in this sample. Although it has not been widely studied in Brazil, the evaluation of the vascular structure and function measured by PWV can be useful for the identification of early vascular involvement in children. Therefore, the contribution of this research on the discussion of children's health is timely, particularly regarding the identification of future cardiovascular problems.

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