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RESEARCH ARTICLE

Increases in Peripheral Systolic Pressure Levels and Z-score Associate Gradual Aortic Pressure Increase and Functional Arterial Impairment in Children and Adolescents

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Abstract: ***Background*:** Arterial changes associated with children and adolescents high blood pressure (HBP) states would vary depending on the arterial type, arterial indexes considered and/or on blood pressure (BP) levels. Aims: To determine in children and adolescents: 1) if there is gradual structural-functional arterial impairment associated with gradual peripheral (brachial) systolic BP (pSBP) level or z-score increases, and 2) whether subjects with HBP levels and those with normal BP differ in the profiles of arterial changes associated with pSBP deviations.

***Methods*:** 1005 asymptomatic children and adolescents were included. Clinical, anthropometric and arterial non-invasive evaluations were performed. Heart rate, brachial BP, aortic BP and wave-derived parameters (*i.e.* augmentation index), carotid and femoral diameters, blood velocities and elastic modulus, carotid intima-media thickness and aortic pulse wave velocity, were obtained. Two groups were assembled: Reference (without cardiovascular risk factors (CVRFs); n=379) and HBP (n=175). Additionally, subjects were ascribed to groups according to their pSBP z-scores (z-score≤0, 0<z-score<1 or z-score≥1). Age and sex-related mean and standard deviation equations were obtained for each variable (Reference group). Using those equations, data (entire population) were converted into z-scores. Groups were compared (absolute and z-scored variables) before and after adjusting for cofactors (ANOVA/ANCOVA). Linear regression analyses were done considering: pSBP and z-pSBP (independent) and absolute levels and z-scores for hemodynamic and arterial indexes (dependent variables). Differences in hemodynamic and arterial levels and z-scores variations (dependent) associated with variations in pSBP and z-pSBP (independent variable) were assessed. The slopes of the models for Reference and HBP groups were compared.

***Conclusion*:** HBP states associate hemodynamic and arterial changes not explained by exposure to other CVRFs, anthropometric or demographic factors. The higher the pSBP deviations from age- and sex-expected mean value in the Reference group, the higher the hemodynamic and arterial indexes deviation. The pSBP-related variations in hemodynamic and arterial indexes would not differ depending on whether HBP states are present or not.

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1. INTRODUCTION

The prevalence of high blood pressure (HBP) states in children and adolescents has increased, paralleled by an increase in overweight and obesity, diabetes and unhealthy behaviors (*i.e.* sedentarism) [1-8]. Despite the clinical manifestations of the atherosclerotic disease are expected in the adult life, it is well known that the atherosclerotic process begins earlier in association with the exposure to cardiovascular risk factors (CVRFs) during childhood [1, 2, 5-13]. Then, identifying exposed subjects and controlling CVRFs in early life would be of value not only due to the recognized

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tracking phenomena to adult life, but also due to vascular impairment would begin and develop in childhood.

Up to now, it has been recognized that hypertensive states in childhood and adolescence are associated with target organ damage (TOD), which is frequently already present at the time of hypertension diagnose [7, 8]. Structural and functional arterial changes observed in association with HBP states during childhood and adolescence characteristically (but not only) include increased wall stiffness and thickness [9, 10]. Those changes have been proposed as an intermediate step in a continuous deleterious process [9] that could result in established arterial disease and cardiovascular events [5].

Several arterial parameters, non-invasively obtained, could be of value in TOD diagnose. Those parameters provide clinically useful information about early structural and functional arterial changes associated with vascular damage, atherosclerosis development and/or increased cardiovascular risk. Recognizing HBP states and the associated TOD during childhood and adolescence is essential since risk control and preventive strategies would be more effective in early stages of the vascular disease process [3, 4, 9, 14-17].

Vascular changes associated with HBP states would vary depending on the vessel, the parameter considered and/or on blood pressure (BP) levels. In addition, as CVRFs cluster, at the time of evaluating high BP-related vascular changes (*i.e.* TOD) it is necessary to take into account the exposure to other risk factors that could contribute to the observed changes. Thus, an adequate vascular evaluation, diagnose and prevention in the context of HBP requires knowing the relationship between BP levels and arterial properties (with independence on other CVRFs effects), and identifying the parameters more sensitive to BP increase [18-22].

This work aims were to determine in asymptomatic children and adolescents: (1) if there is gradual structural and functional arterial impairment associated with gradual peripheral (brachial) BP z-score increases, and (2) whether subjects with hypertensive BP levels and those with normal BP differ in the profile of arterial changes associated with brachial BP z-score increases. To fulfill our aims, the relationships between vascular parameters and BP deviations were analyzed controlling for other CVRFs.

2. MATERIALS AND METHOD

2.1. Study Population

CUiiDARTE is a Uruguayan Interdisciplinary Center and Program (supported by the Public Health Ministry, the National Agency for Research and Innovation and the Republic University), aimed at evaluating and early diagnosing arterial disease in children, adolescents and adults [11, 13, 17, 23]. CUiiDARTE Project is a population-based study in which subjects are submitted to a sequence of evaluative instances: medical interview, laboratory measurements and cardiovascular non-invasive evaluation. Data considered in this work were selected from CUiiDARTE Database and belong to children, adolescents and young asymptomatic adults recruited in the community. Subjects aged under 21 years were considered eligible for the present study (n=1005). Included subjects met the following criteria: none of them was taking medications (antihyperlipidemic, antihypertensive, antidiabetic, antithrombotic) and none had congenital, chronic or infectious diseases at the time of the study. The study protocol conforms to the 1975 Declaration of Helsinki and was approved by the Institution's Ethics Committee. Written informed consent was obtained from the studied subjects, their parents or legal custodian.

Initially, two groups were defined: Reference group and HBP group. The Reference group (n=379, mean age: 16 years; range: 5.1-21 years; 200 females) included subjects without previous diagnoses of hypertension, HBP levels, diabetes, dyslipidemia, tobacco use, obesity, overweight or underweight. Inclusion criteria for HBP group (n=175, mean age 14 years, range 4.2-21 years; 79 females) were known hypertension and/or BP levels >95th percentile for age, sex and body height during the study, for subjects under 16 years of age, and for subjects aged 16 and older inclusion criteria were known hypertension or BP$\geqslant$140/90 mmHg during the study [9].

To analyze deviations in hemodynamic and arterial parameters associated with peripheral (brachial) systolic BP (pSBP) deviations, subjects were divided into three groups defined according to pSBP z-score: Group 1 (n=375) included subjects with z-scores $\leqslant$0; those with z-scores between 0 and 1 were included in Group 2 (n=276) and subjects with z-scores >1 were assigned to Group 3 (n=354).

2.2. Medical Interview and Anthropometric Evaluation

Before cardiovascular evaluation, a clinical interview was conducted in order to assess CVRFs exposure. Children were classified as sedentary when the physical activity they performed was lower than a moderate intensity physical load. Dyslipidemia and diabetes were considered present if they had been previously diagnosed according to the corresponding guidelines. Body weight and height were measured and body mass index (BMI) was calculated as the weight-to-squared height ratio. In subjects under 18 years-old BMI was converted into age- and sex- related z-scores using WHO reference values [24].

Participants were asked to refrain from exercise, smoking, caffeine, alcohol, liquid (except water) or food intake four hours before evaluation. Studies were done in a temperature-controlled (~22°C) room, with subjects in the supine position, after fifteen minutes of rest (to achieve steady hemodynamic conditions).

2.3. Heart rate, Peripheral (Brachial) and Central Aortic BP Assessment and Wave Reflection Parameters

Heart rate (HR) and peripheral systolic (pSBP) and diastolic BP (pDBP) were obtained at 8–10 minutes intervals (oscillometric device, HEM-4030; Omron Healthcare Inc., USA). Peripheral brachial pulse pressure (pPP=pSBP-pDBP) and mean BP levels (MBP=pDBP+pPP/3) were calculated.

To assess central aortic BP (cBP) and wave reflection parameters, radial artery BP waveforms were recorded using applanation tonometry (SphygmoCor-CvMS v.9, AtCor Medical, NSW, Australia) [25]. Acquired pressure waves were calibrated using pDBP and calculated pMBP and a generalized transfer function (GTF) was used to synthesize

the corresponding central aortic BP (cBP) waveform and to obtain central systolic, diastolic and pulse pressure levels (cSBP, cDBP, cPP). Only high quality recordings (operator index >75) and satisfactory waveforms (visual inspection), were considered.

By means of pulse wave analysis (PWA) the first (P1) and second (P2) peaks in the aortic BP wave were identified and their height and time were determined. Then, the difference between P2 and P1 was computed as augmented pressure (AP), which was used to quantify central aortic augmentation index (AIx, AIx= AP/cPP). Since AIx depends on HR, the index normalized for 75 beats/minute (AIx@75) was calculated [25]. Central AIx is a measure of the reflections´ contribution to the aortic pressure wave amplitude. AIx depends on the timing and magnitude of the reflected wave and is influenced by the compliance and structure of vessels distal to the site of measurement, as well as by the distance to the reflection sites. Thus, greater AIx values indicate increased reflections and/or earlier return of reflected waves due to increased arterial stiffness and/or closer reflection sites. The sub-endocardial viability ratio (SEVR), an index of myocardial oxygen supply and demand, was calculated as the ratio between systolic and diastolic areas beneath the aortic BP wave.

2.4. Local Arterial Stiffness and Carotid Intima-media Thickness (B-Mode Ultrasonography)

Left and right common carotid (CCA) and femoral (CFA) arteries were analyzed (B-Mode and Doppler ultrasound, 7–13 MHz linear transducer, M-Turbo, SonoSite Inc., Bothell, WA, USA). Blood flow velocity patterns were analyzed and several parameters were computed: peak systolic velocity (PSV, for both arteries), end-diastolic velocity (EDV, for CCA) and peak reversal (backward) velocity (PRV, for CFA). Sequences of images (videos, at least 30 seconds in duration) were obtained from CCA and CFA in B-Mode (longitudinal views). At least three sequences per artery were obtained and stored for off-line analysis.

Beat-to-beat diameter waveforms were obtained using automatic border detection software [26]. Peak systolic (Sys D) and end diastolic (DD) arterial diameters were obtained averaging at least twenty beats. CCA diameter was measured one centimeter proximal to the bulb, and CFA diameter in the penultimate centimeter (straight segment) proximal to the bifurcation.

CCA and CFA pressure-strain elastic modulus (EM) was calculated as: EM=PP/((Sys D-DD)/DD). Central PP was used to calculate CCA EM (CEM), while peripheral PP was used to calculate CFA EM (FEM) [27, 28].

CCA intima-media thickness (CIMT) was assessed (border detection software) in the posterior wall, in a centimeter proximal to the bifurcation. CIMT was measured at end of diastole and the value considered was the mean of at least six measurements from 3 different sequences (videos) [11, 13].

2.5. Regional Arterial Stiffness: Pulse Wave Velocity

Carotid-femoral pulse wave velocity (cfPWV) was determined to evaluate aortic stiffness (SphygmoCor-CvMS v.9, AtCor-Medical, NSW, Australia). SphygmoCor system allowed obtaining cfPWV from sequential carotid and femoral pulse wave recordings. To this end the pulse transit time was calculated as the difference in the delays between the R wave in the electrocardiographic signal and the foot of the carotid or femoral pulse waves, considering the intersecting tangents algorithm to determine the 'wave foot'. The direct distance between carotid and femoral recording sites was measured and considered as the pulse wave travel distance. Then, cfPWV was calculated as the pulse wave travel distance divided by the pulse wave transit time. Thereafter, ´real´ cfPWV was obtained multiplying the measured cfPWV by a distance scaling factor of 0.8 [26]. The PWV values used for analysis were the mean of 3 different measurements, considered valid if the coefficient of variation was <10%.

2.6. Data Analysis and Statistics

A step-wise data analysis was done. Firstly, age and sex-related mean and standard deviation (SD) equations were determined for each arterial variable (dependent variable) in the Reference population. To this end, parametric regression methods based on fractional polynomials (FPs) were implemented in MedCalc Software (MedCalc, Ostend, Belgium) [16, 17]. Fitting of the different FPs based models was assessed using an iterative procedure (generalized least squares, GLS). Models fit was deemed appropriate if the z-scores (model error) were normally distributed, with a mean of 0 and a SD of 1, randomly scattered above and below 0 when plotted against age. The best-fitted curves, considering visual and mathematical criteria (Kurtosis and Skewness coefficients) were selected. The equations obtained enabled to estimate specific mean and SD for the different variables. Then, using the equations individual data (for the entire population) were typified, that is to say, converted into z-scores, dimensionless numbers obtained by subtracting the population mean from an observation and dividing the result by the population SD.

Two-tailed unpaired Student's t-tests and covariance analyses (ANCOVA) were used to compare and estimate mean differences between Reference and HBP groups. Analyses were done considering typified (z-scores) and non-typified (raw) variables. ANOVA plus Bonferroni Test and ANCOVA were used to compare before and after (respectively) covariate adjustment, the groups defined considering pSBP z-scores.

Finally, linear regression analyses were done considering pSBP levels and pSBP z-scores (z-pSBP) as explanatory (independent, x-axis) variables and the absolute levels and z-scores obtained for the hemodynamic and arterial parameters as dependent variables (y-axis). Differences in the variations in hemodynamic and arterial parameters levels and z-scores (dependent variables) associated with variations in pSBP and z-pSBP (explanatory variables), were assessed, comparing the slopes of the models obtained for the different groups (Reference vs. HBP; test for regression slopes homogeneity).

Continuous and categorical variables were expressed as mean±SD or percentage, respectively. Data analysis was done using MedCalc Statistical Software (version 14.8.1. MedCalc Inc., Ostend, Belgium) and SPSS Software

Table 1. Demographic, hemodynamic and arterial parameters: non typified variables.

	Before Adjustment			After Adjustment*		
	Reference Group	HBP Group		Reference Group	HBP Group	
	MV ± SE	MV ± SE	P value	MV ± SE	MV ± SE	P value
n (% females)	379 (52.8)	175 (44.9)	0.342	379 (52.8)	175 (44.9)	0.342
Age (years)	16.02 ± 0.21	13.96 ± 0.34	**<0.001**	--------	--------	--------
Weight (Kg)	53.02 ± 0.73	59.98 ± 1.71	**<0.001**	--------	--------	--------
Height (m)	1.58 ± 0.01	1.54 ± 0.01	0.110	--------	--------	--------
BMI (Kg/m^2)	20.39 ± 0.13	24.21 ± 0.41	**<0.001**	--------	--------	
Hypertension (%)	0.0	45.1	**<0.001**	0.0	45.1	**<0.001**
Dyslipidemia (%)	0.0	13.7	**<0.001**	--------	--------	--------
Diabetes (%)	0.0	0.0	--------	--------	--------	--------
Obesity (%)	0.0	37.1	**<0.001**	--------	--------	--------
Smoking (%)	0.0	6.8	**<0.001**	--------	--------	--------
HR (beats/minute)	72 ± 1	80 ± 1	**<0.001**	73 ± 1	80 ± 1	**<0.001**
pSBP (mmHg)	112 ± 1	125 ± 1	**<0.001**	112 ± 1	126 ± 1	**<0.001**
pDBP (mmHg)	62 ± 1	68 ± 1	**<0.001**	62 ± 1	70 ± 1	**<0.001**
aSBP (mmHg)	96 ± 1	105 ± 1	**<0.001**	95 ± 1	107 ± 1	**<0.001**
aDBP (mmHg)	63 ± 1	70 ± 1	**<0.001**	63 ± 1	71 ± 1	**<0.001**
aMAP (mmHg)	78 ± 1	86 ± 1	**<0.001**	78 ± 1	88 ± 1	**<0.001**
aPP (mmHg)	33 ± 0	36 ± 1	**0.010**	33 ± 0	36 ± 1	**0.002**
AP (mmHg)	-0.02 ± 0.16	-0.40 ± 0.29	0.258	-0.01 ± 0.19	-0.24 ± 0.34	0.576
AIx (%)	0.82 ± 0.49	-0.43 ± 0.77	0.188	0.82 ± 0.53	0.03 ± 0.94	0.508
AIx@75 (%)	-0.29 ± 0.57	1.97 ± 0.80	**0.037**	-0.21 ± 0.55	2.20 ± 0.98	0.052
SEVR	139.86 ± 1.71	124.04 ± 2.42	**<0.001**	136.68 ± 1.83	132.11 ± 3.23	0.264
CCA Sys D (mm)	6.43 ± 0.03	6.44 ± 0.04	0.867	6.48 ± 0.04	6.34 ± 0.05	0.073
CCA DD (mm)	5.73 ± 0.03	5.74 ± 0.04	0.901	5.77 ± 0.04	5.66 ± 0.05	0.170
CCA EM (mmHg)	427 ± 8	508 ± 22	**0.004**	421 ± 12	500 ± 17	**0.012**
CCA IMT (mm)	0.45 ± 0.01	0.47 ± 0.01	0.111	0.45 ± 0.01	0.46 ± 0.01	0.303
CCA PSV (cm/s)	113 ± 1	125 ± 2	**<0.001**	115 ± 1	121 ± 2	**0.030**
CCA EDV (cm/s)	28 ± 1	29 ± 1	0.934	29 ± 1	29 ± 1	0.572
CFA Sys D (mm)	6.51 ± 1	6.63 ± 0.09	0.420	6.48 ± 0.06	6.60 ± 0.09	0.333
CFA DD (mm)	6.09 ± 1	6.21 ± 0.09	0.427	6.06 ± 0.06	6.18 ± 0.09	0.344
CFA EM (mmHg)	821 ± 21	963 ± 34	**0.008**	818 ± 32	939 ± 46	**0.049**
CFA PSV (cm/s)	123 ± 2	138 ± 2	**<0.001**	127 ± 2	131 ± 3	0.290
CFA PRV (cm/s)	-31 ± 1	-26 ± 1	**<0.001**	-32 ± 1	-25 ± 1	**<0.001**
cfPWV (m/s)	5.68 ± 0.05	5.73 ± 0.08	0.614	5.52 ± 0.05	6.10 ± 0.07	**<0.001**

MV: mean value. SE: standard error. HBP: high blood pressure group. BMI: body mass index. HR: heart rate. Sys D: systolic diameter. DD: diastolic diameter. SBP, DBP, MAP and PP: systolic, diastolic, mean and pulse pressure, respectively. Prefix "p" and "a": peripheral (brachial) and aortic. AP: augmented pressure; AIx: augmentation index. AIx@75: AIx normalized for 75 beats/minute. SEVR: subendocardial viability ratio. EM: elastic modulus. IMT, intima-media thickness. PSV: peak systolic blood flow velocity. EDV, end diastolic blood flow velocity. PRV: peak reversal blood flow velocity. CCA and CFA: common carotid and femoral artery, respectively. cfPWV: carotid-femoral pulse wave velocity. * Controlled (adjusted) by sex, age, anthropometric data and cardiovascular risk factors (except Hypertension) using ANCOVA. Statistical threshold: $p<0.05$.

Table 2. Demographic, hemodynamic and arterial parameters: typified (z-score) variables.

	Before Adjustment			After Adjustment**		
	Reference Group z-score	HBP Group z-score		Reference Group z-score	HBP Group z-score	
	MV ± SD	MV ± SD	P value	MV ± SD	MV ± SD	P value
HR (SD)	<0.001 ± 1.015	0.490 ± 1.286	**<0.001**	0.029 ± 0.062	0.415 ± 0.108	**0.005**
pSBP (SD)	<0.001 ± 1.019	2.142 ± 1.555	**<0.001**	0.010 ± 0.067	2.115 ± 0.117	**<0.001**
pDBP (SD)	<0.001 ± 1.006	1.231 ± 1.555	**<0.001**	-0.032 ± 0.063	1.248 ± 0.109	**<0.001**
aSBP (SD)	<0.001 ± 1.013	1.831 ± 1.568	**<0.001**	-0.014 ± 0.068	1.816 ± 0.118	**<0.001**
aDBP (SD)	<0.001 ± 1.019	1.294 ± 1.461	**<0.001**	0.001 ± 0.065	1.219 ± 0.114	**<0.001**
aMAP (SD)	<0.001 ± 1.026	1.647 ± 1.490	**<0.001**	-0.017 ± 0.065	1.633 ± 0.113	**<0.001**
aPP (SD)	<0.001 ± 1.020	0.624 ± 1.381	**<0.001**	0.032 ± 0.064	0.582 ± 0.112	**<0.001**
AP (SD)	<-0.001 ± 1.033	-0.187 ± 1.369	0.093	0.016 ± 0.065	-0.175 ± 0.115	0.185
AIx (SD)	<-0.001 ± 1.007	-0.216 ± 1.195	**0.037**	0.021 ± 0.061	-0.228 ± 0.107	0.063
AIx@75 (SD)	<-0.001 ± 1.004	0.042 ± 1.151	0.668	0.005 ± 0.06	0.055 ± 0.105	0.733
SEVR (SD)	<0.001 ± 1.048	-0.361 ± 1.165	**<0.001**	-0.056 ± 0.062	-0.203 ± 0.106	0.275
CCA Sys D (SD)	<0.001 ± 1.028	0.114 ± 1.086	0.318	0.117 ± 0.078	-0.067 ± 0.106	0.205
CCA DD (SD)	<0.001 ± 1.027	0.159 ± 0.994	0.148	0.104 ± 0.075	-0.012 ± 0.103	0.411
CCA EM (SD)	-0.030 ± 1.033	0.628 ± 1.262	**<0.001**	0.029 ± 0.086	0.494 ± 0.120	**0.004**
CCA IMT (SD)	<0.001 ± 1.041	0.449 ± 1.526	**0.002**	0.037 ± 0.100	0.343 ± 0.141	0.053
CCA PSV (SD)	<-0.001 ± 1.053	0.262 ± 1.138	**0.010**	-0.006 ± 0.063	0.291 ± 0.104	**0.025**
CCA EDV (SD)	<-0.001 ± 1.015	-0.289 ± 1.201	**0.005**	-0.039 ± 0.061	-0.182 ± 0.103	0.275
CFA Sys D (SD)	<0.001 ± 0.963	0.397 ± 1.249	**0.003**	0.079 ± 0.091	0.278 ± 0.125	0.243
CFA DD (SD)	<0.001 ± 0.965	0.348 ± 1.278	**0.010**	0.082 ± 0.092	0.226 ± 0.125	0.400
CFA EM (SD)	<0.001 ± 0.993	0.703 ± 1.421	**<0.001**	0.018 ± 0.103	0.700 ± 0.141	**0.001**
CFA PSV (SD)	-0.023 ± 0.960	0.407 ± 1.235	**<0.001**	0.026 ± 0.075	0.306 ± 0.114	0.063
CFA PRV (SD)	<0.001 ± 1.056	0.438 ± 1.246	**0.001**	-0.053 ± 0.081	0.579 ± 0.123	**<0.001**
cfPWV (SD)	<0.001 ± 1.032	0.479 ± 1.124	**<0.001**	-0.09 ± 0,060	0.694 ± 0.101	**<0.001**

MV: mean value. SE: standard error. SD: standard deviation. HBP: high blood pressure group. HR: heart rate. Sys D: systolic diameter. DD: diastolic diameter. SBP, DBP, MAP and PP: systolic, diastolic, mean and pulse pressure, respectively. Prefix "p" and "a": peripheral (brachial) and aortic. AP: augmented pressure; AIx: augmentation index. AIx@75: AIx normalized for HR = 75 beats/minute. SEVR: subendocardial viability ratio; IMT: intima-media thickness. PSV: peak systolic blood flow velocity. EDV, end diastolic blood flow velocity. PRV: peak reversal blood flow velocity. CCA and CFA: common carotid and femoral artery, respectively. cfPWV: carotid-femoral pulse wave velocity. ** Controlled (adjusted) for anthropometric data and cardiovascular risk factors (except for hypertension), Statistical threshold: p<0.05.

(IBM SPSS 20, Inc., Illinois, USA). A value of p <0.05 was considered statistically significant.

3. RESULTS

There were differences in age, weight and BMI between HBP subjects and those from the Reference group Table **1**. In agreement with inclusion criteria, subjects in the Reference group were not exposed to CVRFs. In the HBP group, the prevalence of CVRFs was ~45% for hypertension, ~14% for dyslipidemia ~37% for obesity and ~7% for tobacco use.

HR was higher in the HBP group than in the Reference one (p<0.001) Table **1**. As was expected for both, central and peripheral data, SBP, DBP, MBP (p<0.001) and PP levels were higher (p<0.010) in HBP subjects than in those from the reference group Table **1**.

The differences were significant (p<0.001) even after controlling for sex, age, anthropometric data and CVRFs (except for hypertension) Table **1**. AIx@75 was higher (p<0.001) and SEVR lower (p=0.037) in HBP subjects, reinforcing the findings of hemodynamic conditions associated with increased ventricular load in that population Table **1**. After covariate adjustment, the differences in AIx@75 and SEVR between Reference and HBP groups did not reach statistical significance (p=0.052 for AIx@75). Similar results were obtained for wave-derived indexes when comparing Reference and HBP groups considering z-scores (typified variables), with and without covariate adjustment Table **2**.

When comparing HBP and Reference subjects´ vascular parameters Table **1**, we found that both, carotid and femoral PSV were higher in the former (p<0.001). When controlling for covariates, only the differences in carotid PSV remained statistically significant (p=0.030). There were non-significant differences in arterial thickness (carotid IMT) or diameters (femoral and carotid) between Reference and HBP groups. Compared to subjects in the Reference group, those in the HBP group showed higher CCA and CFA stiffness (elastic modulus; p=0.004 and p=0.008, respectively) Table **1**. The differences in local arterial stiffness between HBP and reference groups remained significant after covariate adjustment (p=0.012 for CCA, p=0.049 for CFA) Table **1**. Regional aortic stiffness (cfPWV) levels did not show statistically significant differences between HBP and Reference groups before adjusting for covariates (p=0.614). However, after covariate adjustment, higher cfPWV levels were observed in the HBP group (p<0.001) Table **2**.

There were differences in z-IMT and in CFA diameter z-scores (systolic and diastolic) between HBP and Reference subjects (p≤0.01) before covariate adjustment Table **2**. However, when covariate adjustment was considered, the differences between HBP and Reference groups did not reach statistical significance Table **2**.

When considering typified variables, both, local (CCA and CFA elastic modulus) and regional (cfPWV) stiffness values were higher in HBP subjects than in those from the Reference group (p<0.01).Those findings were observed before and after covariate adjustment Table **2**.

Table **3** shows demographic, anthropometric, hemodynamic, arterial parameters and CVRFs prevalence for the groups defined considering z-pSBP. Data were compared before and after covariate analysis. There were not differences in age or body height among groups Table **3**. BMI increased in association with z-pSBP increase. The highest BMI levels and the highest prevalence of obesity were observed in Group 3 Table **3**. As was expected, Groups 3 showed the highest prevalence of hypertension Table **3**.

For both, central and peripheral hemodynamic data, there were differences in SBP, DBP, MBP and PP among groups Table **3**. Compared to subjects in Groups 1 and 2 those in Group 3 showed higher pSBP, pDBP, cSBP, cDBP, cPP and MBP levels (p<0.001). In addition, those hemodynamic parameters were higher in Group 2 than in Group 1 (p<0.001). The differences among groups were observed for typified and non-typified variables; before and after controlling for covariates Table **3**.

The SEVR levels were lower in Group 3 than those observed in Groups 1 (p<0.001) and 2 (p=0.016). Similar results were observed when z-SEVR was analyzed (p<0.001 and p=0.023, for Group 1 vs 3 and for 2 vs. 3, respectively). When data were controlled for covariates, only the differences between Groups 1 and 3 were statistically significant (SEVR p=0.007; z-SEVR p=0.006) Table **3**.

There were no differences in CCA IMT, CCA diameter or in CFA diameter among the groups. CCA and CFA PSV increased from Group 1 to Group 3. For the CCA, the differences in PSV were significant when comparing subjects in Group 1 and those in Groups 2 (p=0.006) and 3 (p<0.001). In turn, there were differences in CFA PSV between Groups 1 and 3 and between Groups 2 and 3 (p<0.01). Similar results were obtained for CFA z-PSV (p<0.01). The differences remained statistically significant after covariate analysis (p<0.01) Table **3**.

Local stiffness levels (carotid and femoral EM) increased from Group 1 to Group 3. For CCA EM, the differences were statistically significant when comparing subjects in Group 1 with those in Groups 2 and 3 (p<0.05) Table **3**. Similar results were obtained when controlling for covariates. When typified CCA EM was analyzed, all the differences among groups were statistically significant (p<0.05) Table **3**. In turn, CFA EM was higher in Group 3 than in Groups 1 and 2, both, before and after covariate adjustment (p<0.01). Similar results were obtained when typified CFA EM was considered (p<0.01) Table **3**.

The highest regional stiffness (cfPWV) levels were observed in Group 3. The differences between Group 3 and Groups 1 and 2 were statistically significant after controlling for covariates (p<0.001) Table **3**. The z-cfPWV showed a gradual increase from Group 1 to Group 3. When z-cfPWV was analyzed the differences were statistically significant when comparing subjects in Group 3 with those in Groups 1 and 2 (p≤0.001) Table **3**. Those findings were similar before and after covariate adjustment (p<0.001) Table **3**.

Table **4** shows data for regression models obtained considering pSBP or z-pSBP as explanatory (independent) variables and the hemodynamic and vascular parameters as dependent ones. In both, Reference and HBP groups, aortic SBP, DBP, MBP and PP showed a positive correlation with pSBP (p<0.01). Similar results were obtained when typified variables were considered in the models. There were no significant differences when the models obtained for the Reference and HBP groups were compared (slope comparisons) Table **4**. Then, the associations between pSBP (or z-pSBP) and the central hemodynamic parameters observed in the Reference group did not show differences with those observed in the context of HBP. Similar results were obtained when comparing models obtained for aortic wave-derived parameters Table **4**.

There were differences in the vascular parameters´ associations with pSBP. The differences varied, depending on the parameter (*i.e*. typified or non-typified) and/or group considered (reference or HBP) Table **4**.

CCA PSV and z-PSV in the Reference group showed a positive association with pSBP (p=0.001) Table **4**. Such association was not observed in HBP group. Femoral artery PSV showed a statistically significant association with pSBP Table **4** in the Reference group, but not in the HBP group. When typified PSV was analyzed opposite results were obtained Table **4**.

As was expected, local arterial stiffness showed a positive correlation with pSBP; then, the higher the pSBP, the stiffer the arteries. However, there were differences depending on the artery analyzed and on whether typified or non-typified variables were considered Table **4**. In the Reference group, the association between CCA stiffness and pSBP

Table 3. Anthropometric, demographic, hemodynamic and vascular parameters for z-pSBP groups: comparisons considering non-typified and typified variables (Part A).

	Low z-pSBP (n=375) (1)	Medium z-pSBP (n=276) (2)	High z-pSBP (n=354) (3)	Comparison before Adjustment (P value)			Comparison after Adjustment* (P value)		
	MV ± SD	MV ± SD	MV ± SD	1 vs 2	1 vs 3	2 vs 3	1 vs 2	1vs 3	2 vs 3
Age (years)	15.62 ± 4,30	15.29 ± 5.53	14.89 ± 4.61	1.000	0.081	0.782	------	------	------
Weight (Kg)	52.12 ± 14,77	56.62 ± 18.41	59.11 ± 19.94	0.005	<0.001	0.261	------	------	------
Height (m)	1.55 ± 0.16	1.56 ± 0.18	1.57 ± 0.18	1.000	0.855	1.000	------	------	------
BMI (Kg/m^2)	20.97 ± 3.61	22.30 ± 2.86	23.33 ± 5.25	0.001	<0.001	0.016	------	------	------
Hypertension (%)	2.4	7.9	12.7	0.563	0.048	0.534	------	------	------
Dyslipidemia (%)	6.1	5.7	7.9	0.761	0.812	0.679	------	------	------
Diabetes (%)	0.0	0.0	0.0	------	------	------	------	------	------
Obesity (%)	10.1	17.3	25.9	0.879	0.045	0.063	------	------	------
Smoking (%	7.2	7.2	7.3	0.927	0.917	0.943	------	------	------
HR (b.p.m)	73 ± 12	74 ± 14	78 ± 14	0.585	<0.001	<0.001	0.166	<0.001	<0.001
z-HR (SD)	-0.10 ± 1.00	0.06 ± 1.13	0.36 ± 1.17	0.223	<0.001	0.002	0.280	<0.001	0.002
pSBP (mmHg)	105.6 ± 6.76	114.7 ± 6.47	125.6 ± 9.76	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
z-pSBP (SD)	-0.80 ± 0.68	0.45 ± 0.28	2.11 ± 1.01	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
pDBP (mmHg)	59.78 ± 6.78	62.85 ± 6.62	68.39 ± 8.25	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
z-pDBP (SD)	-0.38 ± 0.95	0.17 ± 0.91	1.09 ± 1.23	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
aSBP (mmHg)	91.07 ± 7.22	98.30 ± 7.80	106.15 ± 9.62	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
z-aSBP (SD)	-0.70 ± 0.75	0.43 ± 0.71	1.79 ± 1.05	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
aDBP (mmHg)	60.80 ± 6.62	64.30 ± 6.93	69.99 ± 8.49	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
z-aDBP (SD)	-0.40 ± 0.90	0.20 ± 0.96	1.09 ± 1.20	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
aMAP	74.91 ± 5.94	80.15 ± 5.70	87.20 ± 7.74	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
z-aMAP (SD)	-0.60 ± 0.83	0.32 ± 0.75	1.55 ± 1.17	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
aPP (mmHg)	30.20 ± 7.43	34.08 ± 8.51	36.32 ± 8.84	<0.001	<0.001	0.002	<0.001	<0.001	0.001
z-aPP (SD)	-0.30 ± 0.99	0.25 ± 1.02	0.72 ± 1.13	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
AP (mmHg)	0.36 ± 3.10	-0.07 ± 3.33	-0.06 ± 4.03	0.365	0.345	1.000	1.000	1.000	1.000
z-AP (SD)	0.05 ± 0.98	-0.07 ± 1.13	-0.11 ± 1.26	0.457	0.174	1.000	0.614	0.208	1.000
AIx	2.07 ± 9.81	0.50 ± 9.75	0.40 ± 10.07	0.150	0.081	1.000	0.821	1.000	1.000
z-AIx (SD)	0.05 ± 1.01	-0.08 ± 1.13	-0.15 ± 1.10	0.339	0.043	1.000	0.464	0.041	0.998
AIx@75 (%)	0.88 ± 10.74	-0.04 ± 10.81	1.71 ± 10.99	0.880	0.970	0.157	1.000	0.018	0.033
z-AIx@75 (SD)	-0.01 ± 1.00	-0.02 ± 1.06	0.05 ± 1.10	1.000	1.000	1.000	1.000	1.000	1.000
SEVR	139 ± 33	136 ± 32	129 ± 32	0.600	<0.001	0.016	1.000	0.007	0.084
z-SEVR (SD)	0.06 ± 1.11	-0.07 ± 1.06	-0.31 ± 1.09	0.398	<0.001	0.023	1.000	0.006	0.105

MV: mean value. SE: standard error. SD. standard deviation. HBP: high blood pressure group. HR: heart rate. Sys D: systolic diameter. DD: diastolic diameter. SBP, DBP, MAP and PP: systolic, diastolic, mean and pulse pressure, respectively. Prefix "p" and "a": peripheral (brachial) and aortic. AP: augmented pressure; AIx: augmentation index. AIx@75: AIx normalized for HR = 75 beats/minute. SEVR: subendocardial viability ratio; IMT: intima-media thickness. PSV: peak systolic blood flow velocity. EDV, end diastolic blood flow velocity. PRV: peak reversal blood flow velocity. CCA and CFA: common carotid and femoral artery, respectively. cfPWV: carotid-femoral pulse wave velocity.Z: z score. * Controlled (adjusted) for cardiovascular risk factors and for demographic and anthropometric data. Statistical threshold: p<0.05.

Table 3. Anthropometric, demographic, hemodynamic and vascular parameters for z-pSBP groups: comparisons considering non-typified and typified variables (Part B).

	Low z-pSBP (n=375) (1)	Meedium z-pSBP (n=276) (2)	High z-pSBP (n=354) (3)	Comparison before Adjustment (P value)			Comparison after Adjustment* (P value)		
	MV ± SD	MV ± SD	MV ± SD	1 vs 2	1 vs 3	2 vs 3	1 vs 2	1 vs 3	2 vs 3
CCA Sys D (mm)	6.48 ± 0.55	6.48 ± 0.64	6.45 ± 0.65	1.000	1.000	1.000	1.000	0.070	0.195
CCA z-Sys D (SD)	0.09 ± 0.93	0.14 ± 1.12	0.07 ± 1.14	1.000	1.000	1.000	1.000	0.305	0.405
CCA DD (mm)	5.79 ± 0.56	5.79 ± 0.64	5.74 ± 0.64	1.000	1.000	1.000	1.000	0.133	0.136
CCA z-DD (SD)	0.10 ± 0.93	0.18 ± 1.05	0.08 ± 1.11	1.000	1.000	0.919	1.000	0.321	0.219
CCA EM (mmHg)	425 ± 163	439 ± 147	496 ± 244	0.048	<0.001	0.209	0.002	<0.001	0.231
CCA z-EM (SD)	-0.07 ± 1.06	0.29 ± 1.01	0.59 ± 1.12	0.002	<0.001	0.018	0.001	<0.001	0.028
CCA IMT (mm)	0.46 ± 0.06	0.45 ± 0.06	0.46 ± 0.06	1.000	1.000	0.698	1.000	1.000	1.000
CCA z-IMT (SD)	0.15 ± 1.31	0.18 ± 1.26	0.32 ± 1.42	1.000	0.519	0.901	1.000	0.992	0.925
CCA PSV (m/s)	111.99 ± 20.91	117.93 ± 25.33	122.41 ± 24.39	0.006	<0.001	0.064	0.041	<0.001	0.317
CCA z-PSV (SD)	-0.10 ± 1.01	0.11 ± 1.28	0.29 ± 1.10	0.048	<0.001	0.148	0.088	<0.001	0.012
CCA EDV (m/s)	29.20 ± 6.83	29.53 ± 6.55	29.36 ± 7.06	1.000	1.000	1.000	1.000	1.000	1.000
CCA z-EDV (SD)	-0.01 ± 1.12	-0.03 ± 1.17	-0.07 ± 1.12	1.000	1.000	1.000	1.000	1.000	1.000
CFA Sys D (mm)	6.51 ± 1.11	6.50 ± 1.29	6.64 ± 1.20	1.000	0.814	0.822	1.000	0.830	0.577
CFA z-Sys D (SD)	0.10 ± 1.05	0.21 ± 1.15	0.34 ± 1.21	1.000	0.094	0.819	1.000	1.000	1.000
CFA DD (mm)	6.09 ± 1.12	6.06 ± 1.26	6.21 ± 1.19	1.000	0.941	0.753	1.000	0.734	0.670
CFA z-DD (SD)	0.10 ± 1.04	0.15 ± 1.10	0.32 ± 1.20	1.000	0.147	0.466	1.000	1.000	1.000
CFA EM (mmHg)	791 ± 145	776 ± 166	947 ± 164	1.000	<0.001	<0.001	0.902	<0.001	0.010
CFA z-EM (SD)	-0.09 ± 1.03	0.04 ± 0.96	0.49 ± 1.32	0.887	<0.001	0.007	1.000	<0.001	0.002
CFA PSV (m/s)	123 ± 31	125 ± 32	137 ± 34	1.000	<0.001	0.001	1.000	<0.001	0.002
CFA z-PSV (SD)	-0.14 ± 1.00	0.01 ± 1.08	0.43 ± 1.23	0.501	<0.001	<0.001	0.552	<0.001	0.001
CFA PRV (m/s)	-30 ± 13	-30 ± 13	-28 ± 13	1.000	0.979	1.000	1.000	1.000	0.952
CFA z-PRV (SD)	0.13 ± 1.17	0.06 ± 1.12	0.23 ± 1.13	1.000	1.000	0.380	1.000	1.000	0.483
cfPWV (m/s)	5.52 ± 0.96	5.644 ± 1.035	5.81 ± 1.05	0.430	0.001	0.127	0.139	<0.001	<0.001
z-cfPWV (SD)	-0.08 ± 0.99	0.080 ± 1.116	0.42 ± 1.05	0.184	<0.001	<0.001	0.303	<0.001	<0.001

MV: mean value. SE: standard error. SD. standard deviation. HBP: high blood pressure group. HR: heart rate. Sys D: systolic diameter. DD: diastolic diameter. SBP, DBP, MAP and PP: systolic, diastolic, mean and pulse pressure, respectively. Prefix "p" and "a": peripheral (brachial) and aortic. AP: augmented pressure; AIx: augmentation index. AIx@75: AIx normalized for HR=75 beats/minute. SEVR: subendocardial viability ratio; IMT: intima-media thickness. PSV: peak systolic blood flow velocity. EDV, end diastolic blood flow velocity. PRV: peak reversal blood flow velocity. CCA and CFA: common carotid and femoral artery, respectively. cfPWV: carotid-femoral pulse wave velocity. z: z score. * Controlled (adjusted) for cardiovascular risk factors and for demographic and anthropometric data. Statistical threshold: p<0.05.

was statistically significant only when z-EM was considered (p<0.001) Table **4**. On the contrary, in the HBP group typified and non-typified CFA EM showed positive associations with association Table **4**.

There were not significant differences between the Reference and HBP groups when comparing the models obtained for the EM-pSBP relationships. CFA stiffness in the Reference group was positively associated with pSBP levels (p<00.001) Table **4**. When the z-EM was considered, the association was not statistically significant. On the contrary, both, typified and non-typified CFA EM was positively associated with pSBP (p<0.001) Table **4**.

Regional aortic stiffness (cfPWV) showed a positive correlation with pSBP (p<0.001) in the Reference and HBP groups. When typified regional stiffness was considered, the association with pSBP remained statistically significant (p=0.001 in Reference, p=0.043 in HBP group).

Table 4. Association between pSBP or z-pSBP (independent variable) and non-typified and typified hemodynamic and arterial parameters (dependent variables) (Part A).

	Reference Group			HBP Group			β Difference
	Model	**R**	**P**	**Model**	**R**	**P**	**P**
HR (b.p.m)	-0.148x+87.735	0.123	**0.022**	-0.037x+85.086	0.033	0.676	0.288
z-HR (SD)	0.150x+0.002	0.152	**0.003**	0.216x+0.010	0.238	**0.003**	0.428
pDBP (mmHg)	0.322x+23.573	0.445	**<0.001**	0.330x+26.931	0.456	0.208	0.804
z-pDBP (SD)	0.493x-0.001	0.500	**<0.001**	0.421x+0.335	0.405	**<0.001**	0.360
aSBP (mmHg)	0.845x+1.594	0.893	**<0.001**	0.785x+7.134	0.848	**<0.001**	0.135
z-aSBP (SD)	0.838x-0.003	0.840	**<0.001**	0.758x+0.227	0.711	**<0.001**	0.160
aDBP (mmHg)	0.349x+24.307	0.439	**<0.001**	0.416x+18.121	0.557	**<0.001**	0.248
z-aDBP (SD)	0.503x+0.001	0.502	**<0.001**	0.473x+0.245	0.481	**<0.001**	0.696
aMAP	0.569x+14.922	0.755	**<0.001**	0.570x+15.413	0.777	**<0.001**	0.989
z-aMAP (SD)	0.764x-0.06E-6	0.760	**<0.001**	0.682x+0.203	0.66	**<0.001**	0.189
aPP (mmHg)	0.496x-22.557	0.549	**<0.001**	0.394x-13.496	0.523	**<0.001**	0.098
z-aPP (SD)	0.338x-0.003	0.339	**<0.001**	0.300x-0.004	0.305	**<0.001**	0.655
AP (mmHg)	-0.047x+5.211	0.133	**0.012**	-0.082x+9.972	0.133	**0.012**	0.221
z-AP (SD)	-0.001x-0.001	0.001	0.986	-0.144x+0.094	0.147	0.078	0.113
AIx (%)	-0.194x+22.524	0.187	**<0.001**	-0.210x+25.681	0.187	**<0.001**	0.844
z-AIx (SD)	-0.023x-0.001	0.023	0.665	-0.085x-0.040	0.098	0.239	0.463
AIx@75 (%)	-0.314x+34.915	0.261	**<0.001**	-0.207x+27.759	0.256	**0.002**	0.235
z-AIx@75 (SD)	0.43x+0.232	0.440	0.41	-0.004x+0.043	0.005	0.955	0.572
SEVR	0.357x+99.812	0.099	0.062	0.170x+102.831	0.07	0.387	0.499
z-SEVR (SD)	-0.114x-0.001	0.110	**0.038**	-0.132x-0.072	0.157	0.056	0.827

MV: mean value. SE: standard error. SD. standard deviation. HBP: high blood pressure group. HR: heart rate. Sys D: systolic diameter. DD: diastolic diameter. SBP, DBP, MAP and PP: systolic, diastolic, mean and pulse pressure, respectively. Prefix "p" and "a": peripheral (brachial) and aortic. AP: augmented pressure; AIx: augmentation index. AIx@75: AIx normalized for HR = 75 beats/minute. SEVR: subendocardial viability ratio; IMT: intima-media thickness. PSV: peak systolic blood flow velocity. EDV, end diastolic blood flow velocity. PRV: peak reversal blood flow velocity. CCA and CFA: common carotid and femoral artery, respectively. cfPWV: carotid-femoral pulse wave velocity. z: z score. Statistical threshold: $p<0.05$ z-pSBP and pSBP, were respectively employed as explanatory variables when typified (z-score) and non-typified hemodynamic and arterial parameters were (respectively) employed as dependent variables in the simple linear regression models.

4. DISCUSSION

The main findings of this work were:

- First, in children and adolescents, HBP states were associated with hemodynamic and arterial wall changes. About this, together with increased central aortic BP levels, HBP states were associated with changes in aortic pulse wave-derived parameters (*i.e*. AIx and SEVR), related with increased ventricular afterload. In turn, both local and regional arterial stiffness showed higher levels in association with HBP states Tables **1** and **2**.
- Second, hemodynamic and arterial changes in the context of children and adolescents´ HBP states would not be explained by exposure to other CVRFs, neither by anthropometric or demographic factors Tables **1** and **2**.
- Third, hemodynamic and arterial parameters showed gradual impairment in association with pSBP levels. Those findings were observed when considering z-SBP groups Table **3** as well as when simple linear regression analyses were done Table **4**. Higher the pSBP deviations from the age- and sex-related mean value in the reference population (that it is to say higher the z-pSBP), higher the hemodynamic and arterial wall parameters deviation. The association between pSBP and hemodynamic or vascular parameters were observed even after covariate adjustment.
- Fourth, when Reference and HBP groups were compared, there were no significant differences in the slopes (sensitivity) of the regression models obtained for the association between pSBP (explanatory variable) and hemodynamic or arterial parame-

Table 4. Association between pSBP or z-pSBP (independent variable) and non-typified and typified hemodynamic and arterial parameters (dependent variables) (Part B).

	Reference Group			HBP Group			β difference
	Model	**R**	**P**	**Model**	**R**	**P**	**Model**
CCA Sys D (mm)	0.007x+5.676	0.109	0.118	0.014x+4.698	0.285	**0.001**	0.233
CCA z-Sys D (SD)	-0.135x-0.003	0.138	**0.045**	0.063x+0.052	0.088	0.332	**0.033**
CCA DD (mm)	0.011x+4.585	0.159	**0.021**	0.015x+3.953	0.307	**<0.001**	0.502
CCA z-DD (SD)	-0.114x-0.004	0.117	0.092	0.063x+0.096	0.097	0.283	**0.048**
CCA EM (mmHg)	9.190x-470.577	0.470	0.222	7.514x-443.679	0.531	**<0.001**	0.651
CCA z-EM (SD)	0.266x-0.036	0.305	**<0.001**	0.289x+0.065	0.36	**<0.001**	0.789
CCA IMT (mm)	0.002x+0.257	0.294	**<0.001**	0.001x+0.356	0.204	**0.031**	0.137
CCA z-IMT (SD)	0.007x+0.001	0.007	0.921	-0.033x+0.539	0.033	0.741	0.735
CCA PSV (m/s)	0.081x+105.025	0.035	**0.001**	-0.073x+134.721	0.04	0.613	0.411
CCA z-PSV (SD)	0.172x-0.009	0.175	**0.001**	0.089x+0.037	0.129	0.118	0.285
CCA EDV (m/s)	-0.074x+37.319	0.109	**0.041**	-0.151x+47.759	0.266	**0.001**	0.164
CCA z-EDV (SD)	0.119x+0.001	0.120	**0.023**	-0.119x-0.091	0.142	0.085	**0.004**
CFA Sys D (mm)	0.058x+0.203	0.469	**<0.001**	0.042x+1.408	0.461	**<0.001**	0.187
CFA z-Sys D (SD)	0.052x-0.001	0.057	0.459	0.133x+0.133	0.171	0.100	0.437
CFA DD (mm)	0.459x-0.164	0.459	**<0.001**	0.044x+0.770	0.485	**<0.001**	0.261
CFA z-DD (SD)	0.033x-0.001	0.036	0.461	0.172x+0.021	0.218	**0.033**	0.181
CFA EM (mmHg)	14.972x-814.194	0.348	**<0.001**	21.756x-1705.337	0.611	**<0.001**	0.107
CFA z-EM (SD)	0.091x+0.003	0.097	0.092	0.370x-0.050	0.416	**<0.001**	**0.009**
CFA PSV (m/s)	-0.519x+180.854	0.162	**0.013**	0.279x+106.427	0.122	**0.190**	**0.007**
CFA z-PSV (SD)	0.062x-0.021	0.066	1.000	0.224x-0.016	0.294	**0.002**	0.076
CFA PRV (m/s)	-0.282x-0.780	0.217	**0.001**	0.056x-0.174	0.177	**0.056**	0.372
CFA z-PRV (SD)	-0.063x-0.002	0.061	0.359	0.057x+0.326	0.073	0.454	0.231
cfPWV (m/s)	0.046x+0.473	0.434	**<0.001**	0.042x+0.506	0.515	**<0.001**	0.532
z-cf PWV (SD)	0.180x+0.001	0.179	**0.001**	0.147x+0.224	0.151	0.043	0.456

MV: mean value. SE: standard error. SD. standard deviation. HBP: high blood pressure group. HR: heart rate. Sys D: systolic diameter. DD: diastolic diameter. SBP, DBP, MAP and PP: systolic, diastolic, mean and pulse pressure, respectively. Prefix "p" and "a": peripheral (brachial) and aortic. AP: augmented pressure; AIx: augmentation index. AIx@75: AIx normalized for HR = 75 beats/minute. SEVR: subendocardial viability ratio; IMT: intima-media thickness. PSV: peak systolic blood flow velocity. EDV, end diastolic blood flow velocity. PRV: peak reversal blood flow velocity. CCA and CFA: common carotid and femoral artery, respectively. cfPWV: carotid-femoral pulse wave velocity. z: z score. Statistical threshold: p<0.05.Z-pSBP and pSBP, were respectively employed as explanatory variables when typified (z-score) and non-typified hemodynamic and arterial parameters were (respectively) employed as dependent variables in the simple linear regression models.

ters Table **4**. Then, pSBP-associated inter-individual variations in hemodynamic and arterial parameters would not differ depending on whether HBP states are present or not. So, in children and adolescents, the arterial wall sensitivity to BP changes would not depend on BP levels.

Similar BP values would be the result of different hemodynamic and vascular conditions, and would represent dissimilar situations in terms of arterial impedance, ventricular load, target organ damage and cardiovascular risk. In adults, different hemodynamic and arterial phenotypes have been identified in association with HBP states. However, in children the information about that issue is scarce [24, 27]. In this work, we found that HBP states, defined taking into account peripheral (brachial) SBP, were associated with central hemodynamic changes, not only in BP levels but also in aortic wave-derived parameters.

In agreement with that, we previously found central BP changes related to peripheral BP increases [23]. In addition, for the different arteries (central or peripheral) and indexes

(local or regional) considered, increased arterial stiffness levels were observed in association with HBP states. Those findings agree with previous works in which higher stiffness levels were described in association with arterial hypertensive conditions [10, 24-26].

Jointly analyzing the stated above it could be said that the value of preventing and controlling peripheral HBP states in children and adolescents would not be ascribed only to avoiding tracking phenomena and cardiovascular risk reduction in adult life. On the contrary, the positive impact of HBP prevention and control would be identified even in early stages of life, taking into account cardiovascular changes in the context of HBP states could be present in childhood and adolescence.

Clustering of CVRFS is a recognized issue [24, 27]. Then, an adequate characterization of the hemodynamic and vascular changes associated with exposure to a given cardiovascular risk requires controlling for other (potential) explanatory factors.

HBP states in children and adolescents are frequently associated with overweight, obesity and/or dyslipidemia. Furthermore, it has been proposed that childhood hypertension would be part of a syndrome and phenotype that includes specific anthropometric and metabolic characteristics [28].

In agreement with that, we previously found that obese children and adolescents showed higher peripheral and central BP levels, even after controlling for other CVRFs exposure [27]. Additionally, obesity was associated with (age-related) increases in local carotid and femoral arterial stiffness [29]. In this work, as was expected the prevalence of CVRFs in subjects in the HBP group was not negligible Table **1**. In turn, subjects included in the Reference population were, by definition, not exposed to CVRFs. Consequently, the associations between BP and the hemodynamic and arterial variables were also analyzed taking into account cardiovascular risk as well as anthropometric parameters as covariates. After covariate adjustment, there were no changes in the hemodynamic or arterial variations observed in association with HBP. Then, in children and adolescents, HBP states per se would associate deleterious changes in the arterial system Tables **1** & **2**.

In this work we opted for analyzing the associations between peripheral BP (particularly HBP states) and hemodynamic and arterial parameters, considering non-typified and typified variables (z-scores). These last, allow analyzing the associations between inter-individual deviations (variations) in pSBP (considering the expected mean for age and sex) and the deviations in hemodynamic and arterial parameters, expressing data movement away from the mean in terms of standard deviation units. As z-scores are expressed in a dimensionless way, it was possible to analyze, comparatively the variables sensitivity to BP deviations. When hemodynamic parameters were analyzed, central (aortic) SBP was among the variables with the highest deviations (*i.e.* z-score and linear regression slope levels) observed in association with increases in z-pSBP Tables **3** and **4**. In turn, functional (*i.e.* CCA EM, CFA EM or cfPWV) rather than structural (*i.e*. arterial diameters or CCA IMT) were the arterial parameters most sensitive to pSBP deviations Tables **3** and **4**. The differences in the arterial parameters sensitivity to BP deviations could be explained by differences in the time of exposure required by structural and functional arterial properties to show variations in association with high pSBP.

Jointly considering the hemodynamic and vascular parameters´ sensitivity to pBP, it could be proposed that central hemodynamic and functional arterial parameters would be of choice at the time of diagnosing and detecting changes associated with HBP states.

It is noteworthy that hemodynamic and vascular deviations associated with pSBP increases were gradual, suggesting that the cardiovascular impairment associated with HBP states evidenced early in childhood would depend not only on the HBP condition per se, but also on the degree of BP increase. In agreement with our findings, Drukteinis *et al*. [30], described hemodynamic and cardiovascular (deleterious) changes in association with pre-hypertensive states in adolescents and young adults. Similar findings were reported by Zhu *et al*. [31]. In turn, Urbina *et al*. [10] and Lurbe *et al*. [24] demonstrated arterial changes associated with pre-hypertension conditions in children and adolescents. Furthermore, PWV changes and differences were observed across BP groups, with increasing values from normotensive to hypertensive conditions [10].

Finally, no statistically significant differences were observed between Reference and HBP groups when comparing the models (simple linear regressions) obtained to describe the relationships between SBP and the hemodynamic and arterial variables. Then, in children and adolescents, vascular sensitivity (vascular inter-individual variations associated to pSBP inter-individual variation) to BP levels would not be modified, but the vascular changes associated with HBP states would depend on the hemodynamic conditions to which the vessels are exposed. Since Reference and HBP subjects showed similar associations between arterial parameters (or z-sores) and pSBP (or z-pSBP), controlling HBP would result (at least in theory) in an improvement in the arterial properties.

CONCLUSION

In children and adolescents, peripheral HBP states associated central hemodynamic and arterial wall changes not explained by the exposure to other CVRFs, anthropometric and/or demographic factors.

Higher the pSBP deviations from age- and sex-related mean value in the Reference population, higher the hemodynamic and arterial parameters deviation.

The pSBP-associated inter-individual variations in hemodynamic and arterial parameters would not differ depending on whether HBP states are present or not. So, in children and adolescents, the inter-individual arterial wall sensitivity to BP changes would be independent of BP levels.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Institution's Ethics Committee: Faculty of Medicine, UdelaR and of the the Centro Hospitalario Hospital Pereira Rossell, ASSE.

HUMAN AND ANIMAL RIGHTS

No animal were used in this research. All humans research procedures followed were in accordance with the standards set forth in the Declaration of Helsinki <https://www.wma.net/policiespost/wma-declaration-of-helsinki-ethicalprinciples-for-medical-research-involving-human-subjects/>principles of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONSENT FOR PUBLICATION

Written informed consent was obtained from the studied subjects, their parents or legal custodian.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper. This work was supported by the Agencia Nacional de Investigación e Innovación (ANII), Espacio Interdisciplinario (EI) and Comisión Sectorial de Investigación Científica (CSIC-Udelar) of the Republic University, Uruguay. Additionally, this work was supported by extrabudgetary funds generated by CUiiDARTE Centre and Project. None of these organizations influenced the study design or collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the manuscript for publication.

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REFERENCES

[1] Falkner B. Hypertension in children and adolescents: Epidemiology and natural history. Pediatr Nephrol 2010; 25: 1219-24.

[2] Falkner B. Recent clinical and translational advances in pediatric hypertension. Hypertension 2015; 65(5): 926-31.

[3] NHLB, 2011. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. Pediatrics 2011; 128(Suppl 5): S213-56.

[4] Steinberger J, Daniels C, Hagberg N, *et al.* Cardiovascular health promotion in children: Challenges and opportunities for 2020 and beyond A scientific statement from the American Heart Association. Circulation 2016; 134: e236-55.

[5] Drozdz D, Kawecka-Jaszcz K. Cardiovascular changes during chronic hypertensive states. Pediatr Nephrol 2014; 29: 1507-16.

[6] Falkner B, Lurbe E, Schaefer F. High blood pressure in children: Clinical and health policy implications. J Clin Hypertens 2010; 12(4): 261-76.

[7] Woroniecki RP, Kahnauth A, Panesar LE, Supe-Markovina K. Left ventricular hypertrophy in pediatric hypertension: A mini review. Front Pediatr 2017; 5: 101.

[8] Lurbe E, Agabiti-Rosei E, Cruickshank JK, *et al.* 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens 2016; 34(10): 1887-920.

[9] Lewis M, Shatat I, Phillips S. Screening for hypertension in children and adolescents: Methodology and current practice recommendations. Medical University of South Carolina, Charleston, SC, USA. Front Pediatr 2017; 5: 51.

[10] Urbina EM, Williams RV, Alpert BS, *et al.* American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young. Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. Hypertension 2009; 54(5): 919-50.

[11] Santana DB, Zocalo A, Ventura I, *et al.* Health informatics design for assisted diagnosis of subclinical atherosclerosis, structural, and functional arterial age calculus and patient specific cardiovascular risk evaluation. IEEE Trans Inf Technol Biomed 2012; 16(5): 943-51.

[12] Litwin M, Niemirska A, Śladowska-Kozlowska J, *et al*. Regression of target organ damage in children and adolescents with primary hypertension. Pediatr Nephrol 2010; 25: 2489-99.

[13] Urbina E, Khoury P, McCoy C, Daniels S, Kimball T, Dolan L. Cardiac and vascular consequences of pre-hypertension in youth. Clin Hypertens (Greenwich) 2011; 13(5): 332-42.

[14] Santana DB, Zócalo YA, Armentano RL. Integrated e-Health approach based on vascular ultrasound and pulse wave analysis for asymptomatic atherosclerosis detection and cardiovascular risk stratification in the community. IEEE Trans Inf Technol Biomed 2012; 16(2): 287-94.

[15] Weber T, Wassertheurer S, Rammer M, Haiden A, Hametner B, Eber B. Wave reflections, assessed with a novel method for pulse wave separation, are associated with end-organ damage and clinical outcomes. Hypertension 2012; 60(2): 534-41.

[16] Engelen L, Bossuyt J, Ferreira I, *et al.* Reference Values for Arterial Measurements Collaboration. Reference values for local arterial stiffness. Part A: Carotid artery. J Hypertens 2015; 33(10): 1981-96.

[17] Bossuyt J, Engelen L, Ferreira I, *et al.* Reference values for arterial measurements collaboration. Reference values for local arterial stiffness. Part B: Femoral artery. J Hypertens 2015; 33(10): 1997-2009.

[18] Laurent S, Cockcroft J, Van Bortel L, *et al.* Expert consensus document on arterial stiffness: Methodological issues and clinical applications. Eur Heart J 2006; 27(21): 2588-605.

[19] Van Bortel L, Laurent S, Boutouyrie P, *et al.* Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens 2012; 30(3): 445-8.

[20] Bia D, Zócalo Y, Farro I, *et al*. Integrated evaluation of age-related changes in structural and functional vascular parameters used to assess arterial aging, subclinical atherosclerosis, and cardiovascular risk in Uruguayan adults: CUiiDARTE Project. Int J Hypertens 2011; 2011: 587303.

[21] Stein JH, Korcarz CE, Hurst RT, *et al.* Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: A consensus statement from the American Society of Echocardiography Carotid Intima-Media thickness task force endorsed by the society for vascular. J Am Soc Echocardiogr 2008; 21(2): 93-111.

[22] Selamet-Tierney ES, Gauvreau K, Jaff MR, *et al.* Carotid artery intima-media thickness measurements in the youth: Reproducibility and technical considerations. J Am Soc Echocardiogr 2015; 28(3): 309-16.

[23] García-Espinosa V, Curcio S, Marotta M, *et al.* Changes in central aortic pressure levels, wave components and determinants associated with high peripheral blood pressure states in childhood: Analysis of hypertensive phenotype. Pediatr Cardiol 2016; 37(7): 1340-50.

[24] Doyon A, Kracht D, Bayazit AK, *et al.* Carotid artery intima-media thickness and distensibility in children and adolescents: reference values and role of body dimensions. Hypertension 2013; 62(3): 550-6.

[25] Stergiou G, Giovas P, Kollias A, *et al.* Relationship of home blood pressure with target-organ damage in children and adolescents. Hypertens Res 2011; 34: 640-4.

[26] Reusz GS, Cseprekal O, Temmar M, *et al.* Reference values of pulse wave velocity in healthy children and teenagers. Hypertension 2010; 56: 217-24.

[27] Castro JM, García-Espinosa V, Curcio S, *et al.* Childhood obesity associates haemodynamic and vascular changes that result in increased central aortic pressure with augmented incident and reflected

wave components, without changes in peripheral amplification. Int J Vasc Med 2016; 2016: 3129304.

[28] Litwin M, Niemirska A. Intima-media thickness measurements in children with cardiovascular risk factors. Pediatr Nephrol 2009; 24(4): 707-19.

[29] García-Espinosa V, Curcio S, Castro J, *et al.* Children and adolescent obesity associates with pressure-dependent and age-related increase in carotid and femoral arteries' stiffness and not in brachial artery, indicative of nonintrinsic arterial wall alteration. Int J Vasc Med 2016; 2016: 4916246.

[30] Drukteinis J, Roman M, Fabsitz R, *et al.* Cardiac and systemic hemodynamic characteristics of hypertension and prehypertension in adolescents and young adults: The strong heart study. Circulation 2007; 115: 221-7.

[31] Zhu H, Yan W, Ge D, *et al.* Cardiovascular characteristics in American youth with pre hyertension. AJH 2007; 20: 1051-7.