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RESEARCH ARTICLE

Forward and Backward Aortic Components and Reflection Indexes in Children and Adolescents: Determinants and Role in High Pressure States

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Abstract: ***Background*:** High blood pressure states (HBP) would differ in wave components and reflections indexes, which could associate clinical and prognostic implications. The study aims: 1) to characterize the association of aortic wave components and reflection parameters (backward [Pb], forward [Pf], Pb/Pf ratio and augmentation index [AIx]) with demographic, anthropometric, hemodynamic and arterial parameters in healthy children and adolescents; 2) to generate multivariate prediction models for the associations, to contribute to understand the main determinants of Pf, Pb, Pb/Pf and AIx; 3) to identify if differences in wave reflection indexes observed in HBP could be explained by differences in the analyzed parameters.

***Methods*:** Healthy children and adolescents (n=816, females: 386; Age: 3-20 years) were studied. Evaluations: central aortic pressure and wave components (Pb, Pf, Pb/Pf and AIx determination with SphygmoCor [SCOR] and Mobil-o-Graph [MOG]); anthropometric assessment; regional arterial stiffness (carotid-femoral, carotid-radial pulse wave velocity [PWV] and PWV ratio); carotid intima-media thickness; carotid and femoral distensbility; cardiac output; systemic vascular resistances (SVR). Simple and multiple regression models were constructed to determine aortic wave parameters; the main explanatory variables. Normotensive and HBP groups were compared. Differences in wave reflection indexes were analyzed before and after controlling for explanatory variables. Equivalences between SphygmoCor and Mobil-O-Graph data were assessed (correlation and Bland-Altman analyses).

***Results and Conclusion*:** There were systematic and proportional differences between the data obtained with SphygmoCor and Mobil-O-Graph devices. Heart rate (HR), peripheral pulse pressure, height and weight were the variables that isolated (simple associations) or combined (multiple associations), showed the major capability to explain interindividual differences in Pf, Pb, Pb/Pf and AIx. Arterial stiffness also showed explanatory capacity, being the carotid the artery with the major contribution. HBP associated higher Pf, Pb, AIx and lower Pb/Pf ratio. Those findings were observed together with higher weight, arterial stiffness and HR. After adjusting for anthropometric characteristics, HR, cardiac output and SVR, the HBP group showed greater Pf and Pb. Then, Pf and Pb characteristics associated with HBP would not be explained by anthropometric or hemodynamic factors. Evaluating wave components and reflection parameters could contribute to improve the comprehension and management of HBP states.

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1. INTRODUCTION

Blood pressure (BP) levels are determined by a complex interaction between hemodynamic and structural cardiac and micro and macrovascular factors. Thus, similar peripheral BP (pBP) levels would be the result of different hemodynamic and vascular characteristics [1, 2], and would represent dissimilar conditions in terms of central aortic BP (cBP), ventricular load, ventricular-arterial coupling, organ damage and cardiovascular risk.

Consequently, knowing pBP levels would not be enough to comprehend central (aortic) hemodynamics, nor to under-

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stand factors contributing to aortic and left ventricle working conditions.

BP levels and waveforms at any site of the arterial tree are the result of the sum of incident (forward, Pf) and reflected (backward, Pb) components. About this, cBP wave amplitude (central pulse pressure, cPP) can be understood as the sum of a Pf traveling from the heart towards the periphery and a Pb that travels in the opposite direction. While aortic Pf is primarily generated by ventricular ejection, and mainly depends on the ventricle and central arteries properties (*i.e.* aortic impedance), Pb components originate in arterial sites where changes in geometry, impedance and wall stiffness occur. Thus Pb components also depend on peripheral arterial properties [1]. Those components summate in their transit and form a composite wave that arrives to the ascending aorta [3]. The classical theory indicates that if the arrival occurs mainly in the (ventricular) diastolic phase, it is beneficial, but if it arrives in systole, it increases aortic systolic BP (cSBP) and ventricular load, adversely influencing the systolic and diastolic functions and could contribute to a detrimental ventricular remodeling [1, 3]. However, it has been recently proposed that during childhood, an early arrival of reflected waves would be necessary for an adequate myocardial growth and development [4].

Wave separation analysis (WSA) could contribute to understand particular central hemodynamic characteristics associated with physiological and pathological conditions. Based on wave separation mathematical models (*i.e.* triangular blood-flow, Windkessel-ARCsolver) [2, 5], it was demonstrated that in adults, aortic Pf and Pb amplitude, Pb/Pf ratio and aortic wave derived indexes (*i.e.* augmentation index, AIx) are predictive of target organ damage, cardiovascular disease and/or events (regardless of pBP levels) [3, 6-8]. The contribution of Pf and Pb components to high BP (HBP) states in middle-aged and elderly populations has been analyzed in several works, and as a result, it has been proposed that interindividual differences in cBP wave components would contribute to the differences in HBP presentation and impact in adults [3, 6-10].

Data regarding variations in cBP wave components and indexes, and their potential contribution to HBP states in children and adolescents are scarce. Considering the recognized age-related differences in HBP, the wave components contribution to those states could differ between adults and children or adolescents [11, 12]. Furthermore, there are several issues related with BP components and determinants in childhood and adolescence waiting to be analyzed. In this regard, it is unknown whether demographic, anthropometric, hemodynamic and/or arterial indexes are associated with Pf and Pb components and/or if they contribute to variations in BP components (*i.e.* Pf and Pb increases) during HBP states in children and adolescents. Knowing the determinants of the cBP wave components and their role during HBP would contribute to improve comprehension and management of HBP states.

The aims of this study were: 1) to characterize the association of aortic Pb, Pf, Pb/Pf ratio and AIx with demographic, anthropometric, hemodynamic and arterial (structural and functional) parameters in healthy children and adolescents; 2) to generate multivariate prediction models for the associations (including demographic, anthropometric, hemodynamic and arterial parameters), that contribute to understand the main determinants of Pf, Pb, Pb/Pf and AIx; 3) to identify if differences in wave reflection indexes observed in HBP states could be explained by differences in demographic, anthropometric, hemodynamic and/or arterial characteristics.

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 vascular evaluation and early diagnosis of arterial disease in children, adolescents and adults [11-14]. 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 and adolescents, recruited in the community (n=816, females: 386; Age:3-20 years). Included subjects met the following criteria: none of them were taking medications (antihyperlipidemic, antihypertensive, antidiabetic and antithrombotic); none had congenital, chronic or infectious diseases at the time of the study; none had carotid and/or femoral atherosclerotic plaques (B-Mode/Doppler vascular ultrasound examination). Exclusion criteria were heart rhythm other than stable sinus rhythm.

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 or their guardians.

2.2. Medical Interview and Anthropometric Evaluation

A clinical interview was conducted before cardiovascular evaluation, to assess cardiovascular risk factors (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 in subjects with the previous diagnosis by their referring medical doctors. Subject body weight and height were measured. 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 [15].

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 supine position, after fifteen minutes of rest in order to achieve a steady hemodynamic state. Heart rate and peripheral systolic (pSBP) and diastolic BP (pDBP) were obtained at 8–10 minutes intervals (oscillometric device, HEM-4030; Omron Healthcare Inc., USA). Peripheral PP (pPP=pSBP-pDBP) and mean BP levels (MBP=pDBP+pPP/3) were calculated.

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2.3. Aortic Pressure and Wave Reflection Parameters (Applanation Tonometry, SphygmoCor System)

To assess cBP and wave reflection parameters, radial artery BP waveforms were recorded using applanation tonometry (SphygmoCor-CvMS v.9, AtCor-Medical, NSW, Australia) [2]. Acquired waves were calibrated (using pDBP and calculated MBP levels) and a generalized transfer function (GTF) was used to synthesize the corresponding cBP waveform. 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 the second (P2) peaks in the BP wave were identified and their height and time were determined (Fig. **1**).

Then, the difference between P2 and P1 was computed (augmented pressure, AP) and used to quantify central aortic augmentation index (AIx) as the ratio between AP and cPP (Fig. **1**). Since AIx depends on heart rate, the index normalized for a 75 beats/minute ($AIx@75_{SCOR}$) was considered [2]. AIx is a measure of the reflections contribution to the pressure wave amplitude. It 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 [1, 2]. Greater AIx values indicate increased reflections and/or earlier return due to increased arterial stiffness and/or closer reflection sites.

Wave components were separated considering a triangular flow model (wave separation analysis, WSA, SphygmoCor software) [2, 5, 8]. Thus, Pf_{SCOR} and Pb_{SCOR} were obtained.

2.4. Aortic Pressure and Wave Reflection Parameters (Oscillometric Recordings, Mobil-O-Graph System)

Left brachial BP levels and waveforms were captured using a cuff-based device (MOG, Mobil-O-Graph, IEM, Stolberg, Germany) [16]. After peripheral BP levels were obtained (oscillometry), the brachial cuff was automatically inflated to DBP and held constant during approximately 10 seconds so as to record brachial BP waves. Then, the central aortic BP wave and levels were obtained by means of an algorithm that integrates arterial impedance and aortic hemodynamics into a mathematical model [8, 16]. Only high-quality recordings (in-device quality index equal to 1 or 2) and adequate waveforms (visual inspection), were considered. By means of PWA and WSA, parameters similar to those obtained using SphygmoCor were obtained ($AIx@75_{MOG}$, Pf_{MOG} and Pb_{MOG}). Cardiac output and systemic vascular resistances were obtained (MOG system).

The previously called Reflection Index Ratio (RIR) [17] or Reflection Magnitude [3] was calculated as the Pb/Pf ratio, enabling assessing the relative contribution of Pb to cPP, regardless of the reflections arrival times and Pf amplitude (Sphygmocor and MOG).

2.5. Regional Arterial Stiffness: Pulse Wave Velocity

Pulse wave velocity (PWV) was determined (SphygmoCor-CvMS v.9, AtCor-Medical, NSW, Australia) to evaluate regional aortic (carotid-femoral PWV, cfPWV) and upper limb (carotid-radial PWV, crPWV) arterial stiffness [2]. The pulse transit time was calculated as the difference in delays between the R wave of the electrocardiographic signal and the foot of the measured waves, considering the intersecting

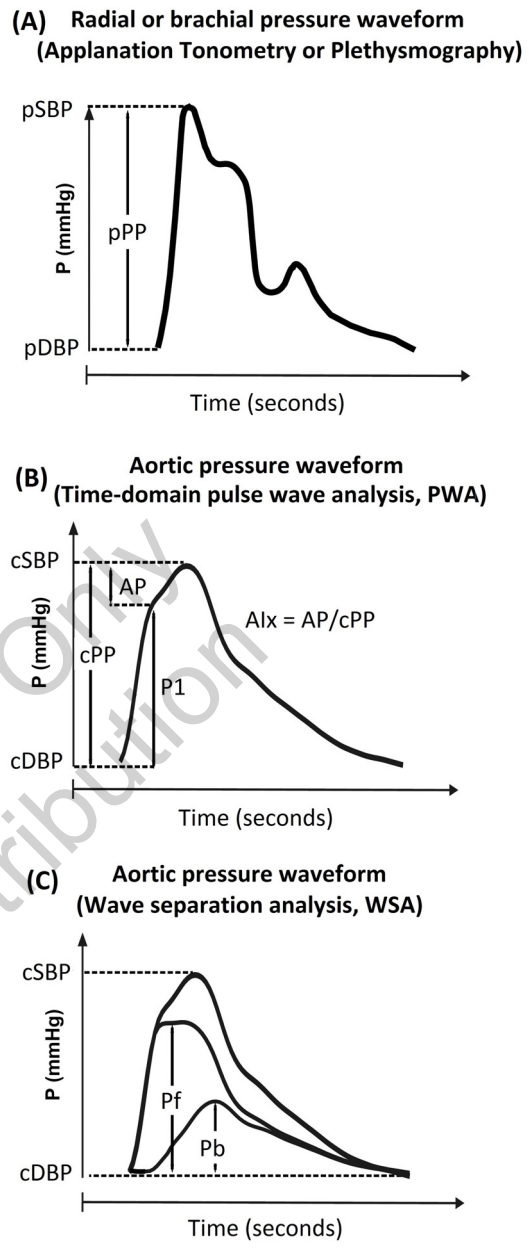

Fig. (1). (**A**) Radial or brachial waveform obtained by applanation tonometry (SphygmoCor or Mobil-O-Graph device, respectively). (**B**) Aortic waveform derived using a general transfer function and aortic augmentation index (AIx) parameter quantified using time-domain pulse wave analysis (PWA). (**C**) Aortic waveform derived using a general transfer function and amplitude of aortic forwad (Pf) and backward (Pb) pressure wave, obtained using wave separation analysis (WSA). pSBP, pDBP and pPP: peripheral systolic, diastolic and pulse blood pressure, respectively. cSBP, cDBP and cPP: central aortic systolic, diastolic and pulse blood pressure, respectively. P1: incident pressure waveheight. AP: augmented pressure. Figure modified of [8].

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tangents algorithm to determine the 'wave foot'. For cfPWV, the pulse wave path length was the distance between carotid and femoral recording sites (direct distance) and for crPWV, it was the direct distance between the radial recording site and the sternal notch. Carotid-femoral distance was multiplied by a scaling factor of 0.8 to obtain "real" cfPWV [2]. The PWV values used for analysis were the mean of three measurements, considered valid if the coefficient of variation was <10%. The PWV ratio, an index used to quantify central-to-peripheral stiffness gradient, was quantified as cfPWV/crPWV [18, 19].

2.6. Carotid Artery Intima-media Thickness and Local Stiffness (B-Mode Ultrasonography)

Left and right common femoral arteries (CFA), internal, external and common carotid (CCA) arteries were analyzed (B-Mode and Doppler ultrasound, 6–13 MHz linear transducer, M-Turbo, SonoSite Inc., Bothell, WA, USA). Blood flow patterns and velocities were determined. Sequences of images (videos, 30 seconds in duration) were obtained from left and right CCA and CFA in longitudinal views (at least three sequences per artery). Videos were stored for off-line analysis. Then, beat-to-beat diameter waveforms were obtained using automatic border detection software. Systolic (SD) and diastolic (DD) arterial diameters considered for analysis were obtained averaging at least twenty beats.

Cross-sectional arterial distensibility (AD) was quantified as AD=((SD−DD)/DD)/PP [1]. Central PP was considered to quantify CCA AD and peripheral PP to determine CFA AD. CCA AD was measured one centimeter proximal to the bulb, and CFA AD in the straight segment of the penultimate centimeter before the bifurcation.

As in the previous works, CCA intima-media thickness (CIMT) was assessed in the posterior wall, in the centimeter proximal to the bifurcation (border detection software) [11, 14]. CIMT was measured at the end of diastole (DD) and the value considered was the mean of at least six measurements from three different sequences [12, 14].

2.7. Data Analysis and Statistics

A four-step analysis was defined. First, considering the lack of a "gold standard" system to quantify cBP (aortic) waveform and wave-derived parameters, we opted for comparing data from SphygmoCor and Mobil-O-Graph, two validated and commercially available systems. It is noteworthy that AIx, Pf, Pb, and Pb/Pf data obtained with both methods have been used interchangeably. However, the systems differ in: a) the way pBP waveforms are determined, b) the calibration method (external vs. self-calibration), c) the GTF applied and in d) the physical-mathematical approach considered to quantify wave-derived parameters. Correlation and equivalence between SCOR and MOG data obtained were assessed performing correlation and Bland-Altman analyses. For this last, the differences between SCOR and MOG data were plotted against their averages. Bland-Altman results allowed evaluating whether the analysis of the associations between BP wave parameters (Pf, Pb, Pb/Pf and AIx) and anthropometric, demographic, hemodynamic or arterial properties could be done with independence on the system used to assess the former. Second, bivariate correlations and simple linear regression models were obtained between wave-derived parameters (dependent variables) and demographic/anthropometric, hemodynamic and arterial parameters (independent variables). Third, multiple linear regression analysis was done to assess the association between wave-derived parameters (dependent variables) and demographic-anthropometric, hemodynamic and/or arterial parameters (independent variables). Regression models were chosen according to the R values obtained in the simple correlations, and grouped into five models:

- Model 1: included hemodynamic parameters (pPP, pSBP and heart rate).
- Model 2: included anthropometric and demographic parameters (age, body weight and height).
- Model 3: included arterial parameters (PWV and CCA AD).
- Model 4: included variables with the highest R coefficient on simple regression analysis considering an independent variable from each sub-group: hemodynamic (pPP), demographic-anthropometric (body weight) and arterial parameter (CCA AD).
- Model 5: included all parameters described above (age, height, weight, pSBP, pPP, HR, cfPWV and CCA AD).

Variables were entered using forced entry method. To avoid multicollinearity, variance inflation factor (VIF) was obtained, verifying its value between 0.2 and 2. The coefficient of determination R^2 was obtained to assess the associations between variables. Fourth, comparisons between normal pBP and HBP groups were done before and after adjusting for anthropometric, hemodynamic and/or arterial variables (ANCOVA). Considering average pBP values, subjects were assigned to one of two groups: (1) normal pBP (NBP, n=577), defined as pSBP and pDBP<95th percentile of American Pediatrics Association (APA) curves reference for sex, age and height (subjects <18 years) or pSBP<140 mmHg and pDBP<90 mmHg in subjects aged 18 and older; (2) HBP (n=239), defined as average pSBP and/or pDBP >95th percentile of APA curves reference for sex, age and body height or pSBP⩾140 mmHg and/or pDBP⩾90 mmHg in subjects aged 18 and older [20].

Data analysis was done using IBM-SPSS software (SPSS Inc. Illinois, USA). Data were expressed as proportions for categorical variables and as mean value±standard deviation for continuous variables. A p value <0.05 was considered to indicate statistical significance.

3. RESULTS

Table **1** shows subjects' demographic, anthropometric, hemodynamic and arterial characteristics. The expected hemodynamic and arterial biomechanical tendencies were observed. About this, pBP, crPWV, CCA AD were higher than cBP, cfPWV (PWV ratio <1.0) and CFA AD, respectively, indicating peripheral BP and arterial stiffness levels were higher than central levels.

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Table 1. Children and adolescents characteristics (n = 816) (Part A).

Female (%)	**47.30**
Age (years)	14.40 ± 4.38
Body Height (m)	1.55 ± 0.18
Body Weight (kg)	55.49 ± 19.15
BMI	22.46 ± 5.02
z-score BMI	1.34 ± 2.04
Smoking (%)	5.5
Dyslipidemia (%)	8.4
Diabetes (%)	0.7
Sedentarism (%)	52.6
Peripheral SBP (mmHg)	115.43 ± 12.21
Peripheral MBP (mmHg)	80.30 ± 8.00
Peripheral DBP (mmHg)	62.74 ± 7.72
Peripheral PP (mmHg)	52.69 ± 10.69
Heart rate (bpm)	74.91 ± 14.13
Cardiac output (liters/minute)	5.31 ± 0.72
SVR (mmHg/liters/minute)	1.04 ± 0.15
Carotid-femoral PWV (m/s)	5.78 ± 0.96
Carotid-radial PWV (m/s)	8.08 ± 1.43[a]
PWV ratio	0.73 ± 0.13
Right CIMT (mm)	0.458 ± 0.05
Left CIMT (mm)	0.459 ± 0.06
AD Right CCA (10^{-3} mmHg^{-1})	4.17 ± 1.69
AD Left CCA (10^{-3} mmHg^{-1})	4.25 ± 1.83
AD Right CFA (10^{-3} mmHg^{-1})	1.55 ± 0.80[b]
AD Left CFA (10^{-3} mmHg^{-1})	1.54 ± 0.91[b]
Tonometry at radial artery (SphygmoCor)	
Central SBP (mmHg)	97.44 ± 10.31[c]
Central DBP (mmHg)	63.62 ± 7.73
Central PP (mmHg)	33.90 ± 8.95[c]
Pf_{SCOR} (mmHg)	33.51 ± 9.86
Pb_{SCOR} (mmHg)	13.38 ± 3.35
Pb_{SCOR}/Pf_{SCOR}	0.41 ± 0.09
$AIx@75_{SCOR}$	0.34 ± 10.78

Table 1. Children and adolescents characteristics (n = 816) (Part B).

Oscillometry at Brachial Artery (Mobil-O-Graph)	
Central SBP (mmHg)	105.40 ± 12.90[c]
Central DBP (mmHg)	67.12 ± 8.04
Central PP (mmHg)	38.28 ± 11.73[c]
Pf_{MOG} (mmHg)	25.80 ± 8.01
Pb_{MOG} (mmHg)	14.72 ± 5.29
Pb_{MOG}/Pf_{MOG}	0.57 ± 0.09
$AIx@75_{MOG}$	13.91 ± 9.89

Values expressed as mean value (MV) ± standard deviaton (SD) or as prevalence. BMI: body mass index. SBP, MBP, DBP and PP: systolic, mean, diastolic and pulse pressure, respectively. SVR: systemic vascular resistances. PWV: pulse wave velocity. CIMT: carotid intima-media thickness. AD: arterial cross-sectional distensibility. CCA and CFA: common carotid and femoral artery, respectively. Pf and Pb: forward and backward components (amplitude) of the aortic pressure wave. AIx@75: aortic augmentation index normalized for a heart rate of 75 beats/minute. SCOR and MOG subheadings indicate parameters obtained with SphygmoCor and Mobil-O-Graph devices, respectively. Statistics: a, b and c indicate significant differences ($p<0.05$; paired two-tailed Student T test) for: carotid-femoral vs. carotid-radial PWV; CCA AD vs. CFA AD and for central vs. peripheral systolic and pulse pressure levels, respectively.

3.1. Comparative Study of Pulse Wave Analysis Systems

There were statistically significant correlations between Pb, Pf, Pb/Pf and AIx@75data obtained using SCOR and MOG ($p<0.05$) [Table **2**]. When Bland-Altman analysis was done we did not find equivalence between the systems, but both, systematic and proportional (except for Pb/Pf ratio) errors were detected ($p<0.05$) [Table **2**].

Weight and Pb/Pf ratio were positively associated [Table **3**]. AIx@75 was negatively associated with age, height, weight and BMI, and positively associated with female sex [Table **3**].

Pf and Pb (obtained with SCOR or MOG) were negatively associated with pDBP (without reaching statistical significance when considering PbSCOR, $p=0.634$) and HR. Pf was (for both devices) negatively associated with SVR. The associations between Pf or Pb and CO, pSBP, pPP, and pMBP were positive for both devices; without reaching statistical significance when considering pMBP and Pb_{MOG} [Table **4**]. HR and SVR were positively associated with Pb/Pf ratio, disregard of the system employed (SCOR or MOG). When SCOR data were considered, Pb/Pf ratio was positively associated with pSBP, pDBP and pPP, while the association with CO was negative [Table **4**]. AIx@75 was negatively associated with pSBP, pPP and CO and positively related with pDBP, HR and SVR [Table **4**].

Pf and Pb (MOG and SCOR derived data) showed a negative association with CCA AD and CFA AD, and a positive association with cfPWV, PWV ratio and CIMT [Table **4**]. The associations between Pb/Pf ratio and arterial parameters differed depending on the system considered (SCOR or MOG). AIx@75 was negatively associated with cfPWV, PWV ratio and CIMT, and positively associated with CCA AD and CFA AD, disregard of the system used.

3.2. Multivariate Models: Analysis of Aortic Wave Parameters´ Predictors

Table **5** shows the multivariate models used to explain Pf, Pb, Pb/Pf and AIx@75 (dependent variables), considering:

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Table 2. Correlation and Bland & Altman analysis: comparison between wave reflection parameters obtained by Sphygmocor and Mobil-O-Graph device.

		Forward Wave (Pf, mmHg)	Backward Wave (Pb, mmHg)	Pb/Pf Ratio	Aix@75
Bivariate correlation	Equation	y = 16.161 + 0.696 x	y = 8.489 + 0.343 x	y= 0.225+0.325 x	y =-7.423+0.482 x
	R	0.57	0.54	0.37	0.45
	P value	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Differences (SCOR-MOG)	Arithmetic mean	8.26	-1.29	-0.16	-14.53
	95% C.I.	7.522 to 9.000	-1.678 to -0.900	-0.169 to -0.151	-15.401 to -13.658
	P (H_0: Mean=0)	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
	SD	8.59	4.52	0.11	10.49
	Lower limit	-8.57	-10.14	-0.37	-35.09
	95% C.I.	-9.832 to -7.304	-10.805 to -9.475	-0.382 to -0.351	-36.581 to -33.601
	Upper limit	25.09	7.56	0.05	6.03
	95% C.I.	23.827 to 26.355	6.897 to 8.226	0.0307 to 0.0618	4.542 to 7.522
	Equation	y = 0.233 + 0.266 x	y = 6.756 + -0.564 x	y = -0.201+0.082 x	y= -15.222+0.107 x
Intercept	Coefficient	0.23	6.76	-0.20	-15.22
	SE	1.42	0.67	0.03	0.56
	t-value	0.16	10.14	-6.34	-27.33
	P value	0.870	**<0.0001**	**<0.0001**	**<0.0001**
	95% C.I.	-2.5638 to 3.0306	5.4471 to 8.0658	-0.2633 to -0.1387	-16.3169 to -14.1284
β1 (Slope)	Coefficient	0.27	-0.56	0.08	0.11
	SE	0.05	0.05	0.06	0.05
	t-value	5.83	-12.50	1.30	2.05
	P value	**<0.0001**	**<0.0001**	0.196	**0.041**
	95% C.I.	0.1767 to 0.3562	-0.6532 to -0.4758	-0.04269 to 0.2079	0.004370 to 0.2098

Pf and Pb: forward and backward components (amplitude) of aortic pressure wave. AIx@75: aortic augmentation index normalized for a heart rate of 75 beats/minute. SCOR and MOG indicate parameters obtained with SphygmoCor and Mobil-O-Graph devices, respectively. C.I.: confidence interval. SD: standard deviation. β1: regression coefficient (slope). SE: standard error. A $p<0.05$ was accepted as statistically significant. Bivariate correlation: y = SCOR value; x = MOG value.

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(a) hemodynamic variables (Model 1); (b) demographic and anthropometric variables (Model 2); (c) arterial variables (Model 3); (d) the variables with the highest individual coefficient of determination in Models 1-3 (Model 4) and (e) all the studied variables (Model 5).

Heart rate and pPP were the hemodynamic variables (Model 1) able to explain ($p<0.05$) interindividual variations in Pf. Neither demographic-anthropometric (Model 2), nor arterial (Model 3) variables, allowed explaining variations in Pf [Table **5**]. Compared to height, weight showed major association with variations in Pf (Model 2). Approximately 62% of the variation in Pf could be explained jointly considering hemodynamic, demographic-anthropometric and arterial variables (Models 4 and 5). Body weight and pPP were the variables with the major contribution to explain variations in Pf (Model 4 and 5) [Table **5**]. As can be seen in Table **5**, the models mostly explained the variations in Pf rather than in Pb.

HR, pPP and SBP allowed explaining ~40% of the variations in Pb when SCOR was used. When MOG data were considered, ~46% of the variations in Pb could be explained by pPP and HR. When anthropometric-demographic (Model 2) or arterial (Model 3) variables were considered separately, only ~10-20% of Pb variations could be explained. The inclusion of more variables (Model 4 and 5) did not give further explanation to that given by pPP and HR. When Pb variations were analyzed, age was a non-explanatory variable [Table **5**].

Approximately 20% of interindividual variations in Pb/Pf could be explained by variations in pPP, pSBP and HR (Model 1). When SCOR data were considered, anthropometric-demographic variables explained ~17% of the variation

Table 3. Regression analysis between aortic components and demographic/anthropometric parameters.

		Forward Wave (Pf, mmHg)		Backward Wave (Pb, mmHg)		Pb/Pf ratio		AIx @75	
		Scor	***MOG***	***Scor***	***MOG***	***Scor***	***MOG***	***Scor***	***MOG***
Demographic data									
Gender Female:1 Male:0	Intercept	36.45	28.43	14.13	16.26	0.40	0.57	-2.35	9.84
	β_1	-6.52	-5.28	-1.36	-3.08	0.04	0.00	6.02	8.18
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.939	**<0.001**	**<0.001**
	R	0.34	0.33	0.21	0.29	0.20	0.00	0.28	0.42
Age (years)	Intercept	22.37	17.74	9.81	8.55	0.44	0.52	12.80	25.34
	β_1	0.69	0.53	0.23	0.41	0.00	0.00	-0.81	-0.76
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.106	**<0.001**	**<0.001**	**<0.001**
	R	0.28	0.27	0.28	0.32	0.06	0.17	0.33	0.32
Smoking Yes:1; No:0	Intercept	32.89	25.65	13.26	14.62	0.42	0.57	0.67	14.00
	β_1	2.32	2.57	2.01	1.62	0.03	0.00	0.09	-2.54
	p	0.077	0.054	**<0.001**	0.066	**0.024**	0.967	0.951	0.125
	R	0.06	0.08	0.16	0.08	0.08	0.00	0.00	0.06
Dyslipidemia Yes: 1; No: 0	Intercept	33.08	26.01	13.43	14.89	0.42	0.57	0.44	13.37
	β_1	-0.75	-2.23	-0.27	-1.76	0.01	-0.02	3.50	5.39
	p	0.573	0.052	0.552	**0.020**	0.639	0.167	**0.011**	**<0.001**
	R	0.02	0.08	0.02	0.10	0.02	0.06	0.08	0.16
Diabetes Yes:1; No: 0	Intercept	33.02	25.81	13.42	14.73	0.42	0.57	0.68	13.81
	β_1	1.38	0.80	-1.62	0.04	-0.06	0.002	2.49	5.08
	p	0.751	0.823	0.273	0.986	0.156	0.950	0.576	0.251
	R	0.01	0.01	0.04	0.001	0.05	0.003	0.02	0.05
Sedentarism Yes: 1; No: 0	Intercept	34.34	26.68	13.63	15.35	0.41	0.57	-1.39	12.56
	β_1	-2.30	-2.06	-0.58	-1.53	0.01	-0.01	3.78	2.74
	p	**0.002**	**0.002**	**0.020**	**<0.001**	0.279	0.246	**<0.001**	**0.001**
	R	0.12	0.13	0.09	0.15	0.04	0.05	0.18	0.14
Anthropometric data									
Height (m)	Intercept	-16.44	-6.96	2.45	-6.37	0.70	0.48	47.21	55.20
	β_1	31.29	20.82	6.94	13.40	-0.18	0.06	-29.74	-26.26
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.010**	**<0.001**	**<0.001**
	R	0.51	0.43	0.33	0.42	0.29	0.11	0.48	0.44
Weight (kg)	Intercept	17.77	15.12	10.28	7.88	0.52	0.54	13.03	24.87
	β_1	0.27	0.19	0.06	0.12	0.00	0.00	-0.22	-0.19
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.023**	**<0.001**	**<0.001**
	R	0.48	0.42	0.29	0.41	0.30	0.09	0.37	0.35
BMI ($Kg./m^2$)	Intercept	20.61	17.67	11.15	9.65	0.51	0.56	8.34	19.56
	β_1	0.56	0.36	0.10	0.22	0.00	0.00	-0.34	-0.25
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.391	**<0.001**	**0.002**
	R	0.27	0.22	0.14	0.21	0.19	0.04	0.15	0.12
z-score BMI	Intercept	31.28	24.83	12.82	13.97	0.42	0.56	1.44	14.83
	β_1	0.56	0.18	0.03	0.03	-0.01	0.00	0.32	0.14
	p	**0.010**	0.359	0.725	0.818	**0.005**	0.307	0.147	0.576
	R	0.12	0.05	0.02	0.01	0.12	0.05	0.06	0.03

BMI: body mass index. SBP, MBP, DBP and PP: systolic, mean, diastolic and pulse pressure. SVR: systemic vascular resistances. PWV: pulse wave velocity. CIMT: carotid intima-media thickness. AD: arterial distensibility. CCA and CFA: common carotid and femoral artery. Pf and Pb: forward and backward components (amplitude) of the aortic wave. AIx@75: augmentation index normalized for a heart rate of 75 beats/minute. SCOR and MOG subheadings: parameters obtained with SphygmoCor and Mobil-O-Graph devices, respectively. β1: regression coefficient. R: Pearson coefficient.

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Table 4. Lineal regression analysis between aortic components and haemodynamic/arterial parameters (Part A).

		Forward Wave (Pf, mmHg)		Backward Wave (Pb, mmHg)		Pb/Pf Ratio		AIx @75	
		Scor	***MOG***	***Scor***	***MOG***	***Scor***	***MOG***	***Scor***	***MOG***
Haemodyamic parameters									
Peripheral SBP (mmHg)	Intercept	-19.71	-4.35	-0.86	-3.27	0.63	0.53	28.10	29.32
	β_1	0.46	0.26	0.12	0.15	0.01	0.01	-0.24	-0.13
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.314	**<0.001**	**<0.001**
	R	0.56	0.39	0.44	0.35	0.24	0.04	0.27	0.16
Peripheral DBP (mmHg)	Intercept	40.83	39.43	13.88	23.21	0.35	0.58	-9.42	-5.40
	β_1	-0.12	-0.22	-0.01	-0.14	0.01	0.01	0.16	0.31
	p	**0.018**	**<0.001**	0.634	**<0.001**	**0.018**	0.627	**0.002**	**<0.001**
	R	0.09	0.20	0.02	0.19	0.09	0.00	0.11	0.23
Peripheral MBP (mmHg)	Intercept	10.72	19.57	6.11	11.29	0.48	0.56	8.18	7.29
	β_1	0.28	0.08	0.09	0.04	0.00	0.00	-0.10	0.08
	p	**<0.001**	0.076	**<0.001**	0.140	0.094	0.831	**0.045**	0.128
	R	0.22	0.07	0.21	0.06	0.06	0.01	0.07	0.06
Peripheral PP (mmHg)	Intercept	-1.36	2.90	4.69	0.90	0.57	0.54	20.74	30.60
	β_1	0.65	0.43	0.16	0.26	0.01	0.01	-0.39	-0.31
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.144	**<0.001**	**<0.001**
	R	0.70	0.57	0.51	0.52	0.33	0.06	0.39	0.34
Heart rate (beats/minute)	Intercept	48.80	43.04	21.68	30.48	0.49	0.78	-25.76	-17.91
	β_1	-0.21	-0.23	-0.11	-0.21	0.01	0.01	0.35	0.43
	p	**0.000**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	R	0.28	0.40	0.45	0.31	0.14	0.20	0.42	0.42
Cardiac output (liters/minute)	Intercept	11.85	14.31	11.09	8.95	0.62	0.57	16.89	52.36
	β_1	4.21	2.17	0.48	1.09	-0.04	-0.0001	-3.31	-7.26
	p	**<0.001**	**<0.001**	**0.023**	**<0.001**	**<0.001**	0.987	**<0.001**	**<0.001**
	R	0.30	0.19	0.10	0.15	0.30	0.0007	0.23	0.53
SVR (mmHg/liters/minute)	Intercept	43.83	31.42	11.68	16.09	0.22	0.51	-12.93	-20.80
	β_1	-9.25	-5.34	1.86	-1.29	0.18	0.05	11.75	33.22
	p	**0.002**	**0.015**	0.066	0.374	**<0.001**	**0.025**	**<0.001**	**<0.001**
	R	0.14	0.10	0.08	0.04	0.29	0.09	0.17	0.50

in Pb/Pf (Model 2). The joint analysis of independent variables (Model 4 and 5) allowed explaining ~37 to 44% of the variations in Pb/Pf. HR and pPP were explanatory variables for both systems of analysis [Table **5**].

Differences in pBP contributed to explain changes in AIx@75 (~26% for SCOR and ~40% for MOG). Disregard of the system considered, age and height were the demographic-anthropometric explanatory variables (Model 2). Once again, as expected, the highest explanatory levels were obtained with models 4 and 5 [Table **5**].

3.3. Wave Reflection Parameters Determinants and High Blood Pressure States

Compared to NBP subjects, those from the HBP group were younger, showed higher body weight, HR and SVR, and lower CCA AD [Table **6**]. Disregard of the system considered, HBP subjects showed higher cSBP, cDBP, cPP,

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Table 4. Lineal regression analysis between aortic components and hemodynamic/arterial parameters (Part B).

		Forward Wave (Pf, mmHg)		Backward Wave (Pb, mmHg)		Pb/Pf Ratio		AIx @75	
		Scor	***MOG***	***Scor***	***MOG***	***Scor***	***MOG***	***Scor***	***MOG***
Arterial parameters									
Carotid-femoral PWV (m/s)	Intercept	18.16	16.34	9.04	8.02	0.46	0.52	15.78	19.83
	β_1	2.62	1.61	0.74	1.14	-0.01	0.01	-2.68	-1.01
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.021**	**0.024**	**<0.001**	**0.020**
	R	0.25	0.19	0.21	0.21	0.09	0.09	0.24	0.10
Carotid-radial PWV (m/s)	Intercept	36.68	30.71	13.18	17.81	0.36	0.58	0.17	11.31
	β_1	-0.42	-0.61	0.01	-0.40	0.01	0.00	0.02	0.34
	p	0.139	**0.018**	0.883	**0.020**	**0.019**	0.537	0.958	0.282
	R	0.06	0.11	0.01	0.11	0.10	0.03	0.00	0.05
PWV ratio	Intercept	17.77	13.12	9.58	6.18	0.49	0.52	10.46	19.81
	β_1	21.26	17.33	5.10	11.56	-0.10	0.06	-14.05	-7.83
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.001**	**0.040**	**<0.001**	**0.022**
	R	0.28	0.28	0.20	0.29	0.14	0.09	0.17	0.10
Right CIMT (mm)	Intercept	16.54	8.61	8.28	2.97	0.50	0.50	12.79	29.70
	β_1	31.63	34.82	9.97	23.23	-0.14	0.11	-22.63	-30.14
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.066	0.355	**0.005**	**0.013**
	R	0.21	0.23	0.18	0.23	0.09	0.06	0.12	0.15
AD Right CCA (1/mmHg $\times 10^{-3}$)	Intercept	42.44	30.40	15.69	17.01	0.36	0.56	-5.90	10.64
	β_1	-2917.40	-1450.90	-731.71	-823.87	16.35	-0.32	2089.85	1270.63
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.926	**<0.001**	**<0.001**
	R	0.27	0.17	0.13	0.16	0.07	0.01	0.10	0.06
AD Right CFA (1/mmHg $\times 10^{-3}$)	Intercept	36.92	27.59	14.51	15.26	0.40	0.56	-2.14	12.60
	β_1	-3811.07	-2121.66	-1091.33	-1149.95	18.22	-0.21	3232.52	2139.52
	p	**<0.001**	**<0.001**	**<0.001**	**0.004**	**0.005**	0.980	**<0.001**	**0.012**
	R	0.10	0.00	0.06	0.00	0.02	0.00	0.06	0.02

BMI: body mass index. SBP, MBP, DBP and PP: systolic, mean, diastolic and pulse pressure, respectively. SVR: systemic vascular resistances. PWV: pulse wave velocity. CIMT: carotid intima-media thickness. AD: arterial cross-sectional distensibility. CCA and CFA: common carotid and femoral artery, respectively. Pf and Pb: forward and backward components (amplitude) of aortic pressure wave. AIx@75: aortic augmentation index normalized for a heart rate of 75 beats/minute. SCOR and MOG subheadings indicate parameters obtained with the SphygmoCor and Mobil-O-Graph devices, respectively. β1: regression coefficient (slope). R: Pearson coefficient. $p<0.05$ was accepted as statistically significant.

sidered, HBP subjects showed higher cSBP, cDBP, cPP, Pf and Pb. Pb/Pf ratio was lower in HBP than in NBP subjects. HBP subjects showed higher AIx@75 when data from MOG were considered.

Table **7** shows the comparison between NBP and HBP subjects after adjusting (additive adjustment) for: a) anthropometric-demographic characteristics, b) global hemodynamic parameters (HR, CO and SVR), and c) pBP and arterial stiffness. After the first two adjustments, Pf and Pb were still higher in HBP subjects. When HBP and NBP subjects were compared adjusting for pBP and arterial stiffness, the differences in Pb and Pf were non-significant.

4. DISCUSSION

Pf, Pb, Pb/Pf and AIx were evaluated in children and adolescents, aiming at contributing to the knowledge of their

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Table 5. Multiple regression analysis between aortic wave components (dependent variable) and demographic, anthropometric, haemodynamic and/or arterial parameters (independent variable).

	Forward wave (Pf mmHg)		Backward wave (Pb mmHg)		Pb/Pf ratio		AIx@75	
	Scor	***MOG***	***Scor***	***MOG***	***Scor***	***MOG***	***Scor***	***MOG***
	β_1±95% CI	β_1±95% CI	β_1±95% CI	β_1±95% CI	β_1±95% CI	β_1±95% CI	β_1±95% CI	β_1±95% CI
Model 1								
Intercept	----------	21.55±3.03	8.84±1.14	17.61±1.89	0.65±0.03	0.74±0.03	---------	-10.64±3.76
pPP (mmHg)	0.56±0.04	0.43±0.04	0.07±.016	0.21±0.02	-0.01±0.01	----------	-0.26±0.05	-0.27±0.05
pSBP (mmHg)	----------	----------	0.06±.014	----------	0.01±0.01	----------	----------	0.09±0.04
Heart rate (b.p.m)	-0.10±0.02	-0.15±0.02	-0.09±0.01	-0.17±0.01	-0.01±0.01	-0.01±0.01	0.29±0.02	0.38±0.02
R^2	0.502	0.389	0.397	0.464	0.168	0.212	0.261	0.397
Model 2								
Intercept	-17.23±3.85	----------	4.84±1.48	----------	0.79±0.04	0.59±0.04	57.23±4.27	59.34±4.99
Weight (kg)	0.12±0.02	0.08±0.02	0.01±0.01	0.06±0.02	-0.01±0.01	----------	----------	----------
Height (m)	33.75±3.56	22.11±3.80	4.19±1.37	9.93±2.55	-0.31±0.03	----------	-41.67±4.12	-31.33±4.78
Age (years)	-0.65±0.11	-0.41±0.12	----------	----------	0.01±0.01	0.01±0.01	0.52±0.13	0.32±0.15
R^2	0.307	0.221	0.112	0.195	0.166	0.028	0.237	0.197
Model 3								
Intercept	39.50±2.71	26.09±3.11	14.86±1.08	14.54±2.08	0.36±0.03	0.54±0.04	----------	9.21±4.44
cfPWV (m/s)	----------	----------	----------	----------	-0.005±0.005	----------	-1.343±0.522	----------
AD Right CCA ($mmHg^{-1} \times 10^{-3}$)	-3076±234	-1475±253	-669±93	-839±169	20.50±2.89	----------	2153±282	1481±360
R^2	0.330	0.131	0.121	0.097	0.123	0.007	0.142	0.052
Model 4								
Intercept	7.97±2.31	----------	8.15±1.12	----------	0.55±0.03	0.54±0.04	10.14±3.60	29.14±4.54
pPP (mmHg)	0.48±0.03	0.32±0.04	0.12±0.01	0.16±0.03	-0.01±0.01	----------	-0.10±0.05	-0.13±0.06
Weight (kg)	0.08±0.02	0.08±0.02	----------	0.05±0.01	-0.01±0.01	----------	-0.14±0.02	-0.13±0.03
AD Right CCA ($mmHg^{-1} \times 10^{-3}$)	-1386±211	----------	-380±102	----------	8.67±3.21	----------	1201±325	----------
R^2	0.601	0.341	0.231	0.251	0.211	0.003	0.200	0.132
Model 5								
Intercept	----------	----------	16.76±2.44	20.13±4.31	0.79±0.07	0.99±0.09	----------	----------
Age	-0.45±0.13	----------	----------	----------	----------	----------	----------	----------
Weight (kg)	0.05±0.02	0.06±0.03	----------	0.05±0.02	-0.01±0.01	----------	----------	----------
Height (m)	12.53±3.97	----------	-3.74±1.77	----------	-0.16±0.04	-0.16±0.07	-23.63±5.94	-15.57±6.72
pSBP (mmHg)	----------	-0.15±0.05	0.06±0.02	----------	0.01±0.01	----------	----------	0.17±0.07
pPP (mmHg)	0.46±0.04	0.43±0.06	0.07±0.02	0.21±0.03	-0.014±0.01	----------	----------	-0.22±0.07
Heart rate (b.p.m)	-0.05±0.02	----------	-0.10±0.01	-0.13±0.02	-0.013±0.01	-0.01±0.01	0.20±0.03	0.34±0.03
cfPWV (m/s)	----------	----------	----------	----------	0.01±0.01	----------	----------	----------
AD Right CCA ($mmHg^{-1} \times 10^{-3}$)	-1390±218	----------	-440±97	----------	5.91±3.04	----------	895±316	----------
R^2	0.616	0.392	0.372	0.444	0.353	0.237	0.310	0.454

Values are expressed as β1 (slope) and the 95% Confidence Interval (CI). pSBP and pPP: peripheral systolic and pulse pressure; cfPWV: carotid-femoral pulse wave velocity; AD: arterial distensibility; CCA: common carotid artery; Pf and Pb: forward and backward wave components´ amplitude. AIx@75: aortic augmentation index normalized for a heart rate of 75 beats/minute. Scor and MOG indicate parameters obtained with the SphygmoCor and Mobil-O-Graph devices. R^2: coefficient of determination. Only values of significant variables ($p<0.05$) are consigned.

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Table 6. Anthropometric, haemodynamic and vascular properties for normal and high pressure groups.

	NBP (n = 577)	HBP (n = 239)	*p* value NBP vs. HBP
Female (%)	49.70	41.40	**0.030**
Age (years)	15.01 ± 4.18	12.94 ± 4.53	**0.000**
Body Height (m)	1.55 ± 0.17	1.54 ± 0.20	0.224
Body Weight (kg)	53.98 ± 17.39	59.08 ± 22.46	**0.001**
Body mass index (Kg./m^2)	21.77 ± 4.46	24.13 ± 5.84	**0.000**
z-score Body mass index	0.85 ± 1.70	2.36 ± 2.28	**0.000**
Smoking (%)	5.7	5.0	0.521
Dyslipidemia (%)	6.9	12.1	**0.015**
Diabetes (%)	0.5	1.3	0.263
Sedentarism (%)	51.7	54.7	0.445
Peripheral SBP (mmHg)	112 ± 10	123 ± 14	**0.000**
Peripheral MBP (mmHg)	79 ± 7	85 ± 9	**0.000**
Peripheral DBP (mmHg)	62 ± 7	66 ± 9	**0.000**
Peripheral PP (mmHg)	51 ± 9	57 ± 12	**0.000**
Heart rate (bpm)	73 ± 13	78 ± 16	**0.000**
Cardiac output (liters/minute)	5.30 ± 0.70	5.32 ± 0.76	0.723
SVR (mmHg/liters/minute)	1.03 ± 0.15	1.08 ± 0.15	**0.000**
Carotid-femoral PWV (m/s)	5.8 ± 0.9	5.8 ± 1.0	0.699
Carotid-radial PWV (m/s)	8.1 ± 1.4	8.1 ± 1.5	0.848
PWV ratio	0.72 ± 0.13	0.73 ± 0.13	0.588
Right CIMT (mm)	0.456 ± 0.054	0.461 ± 0.055	0.347
Left CIMT (mm)	0.458 ± 0.056	0.462 ± 0.057	0.398
AD Right CCA (10^{-3} mmHg^{-1})	4.30 ± 1.74	3.94 ± 1.58	**0.026**
AD Left CCA (10^{-3} mmHg^{-1})	4.38 ± 1.89	4.01 ± 1.70	**0.035**
AD Right CFA (10^{-3} mmHg^{-1})	1.59 ± 0.82	1.48 ± 0.74	0.163
AD Left CFA (10^{-3} mmHg^{-1})	1.60 ± 0.96	1.43 ± 0.78	0.061
Tonometry at radial artery (SphygmoCor)			
Central SBP (mmHg)	95 ± 9	102 ± 12	**0.000**
Central DBP (mmHg)	63 ± 7	66 ± 8	**0.000**
Central PP (mmHg)	33 ± 8	36 ± 10	**0.000**
Pf_{SCOR} (mmHg)	32 ± 9	37 ± 11	**0.000**
Pb_{SCOR} (mmHg)	13 ± 3	14 ± 4	**0.000**
Reflection Index Ratio (Pb_{SCOR}/Pf_{SCOR})	0.42 ± 0.09	0.40 ± 0.09	**0.004**
$AIx@75_{SCOR}$	0.32 ± 10.63	0.40 ± 11.16	0.926
Oscillometry at brachial artery (Mobil-O-Graph)			
Central SBP (mmHg)	103 ± 11	110 ± 16	**0.000**
Central DBP (mmHg)	66 ± 8	70 ± 9	**0.000**
Central PP (mmHg)	37 ± 11	41 ± 13	**0.001**
Pf_{MOG} (mmHg)	25 ± 7	28 ± 9	**0.000**
Pb_{MOG} (mmHg)	14 ± 5	15 ± 6	**0.038**
Reflection Index Ratio (Pb_{MOG}/Pf_{MOG})	0.58 ± 0.08	0.55 ± 0.10	**0.004**
$AIx@75_{MOG}$	13.3 ± 9.2	15.5 ± 11.4	**0.014**

SBP, MBP, DBP and PP: systolic, mean, diastolic and pulse pressure. SVR: systemic vascular resistances. PWV: pulse wave velocity. CIMT: carotid intima-media thickness. AD: arterial distensibility. CCA and CFA: common carotid and femoral artery. Pf and Pb: forward and backward components of aortic wave. AIx@75: augmentation index normalized for a heart rate of 75 beats/minute. NBP and HBP normotensive and high blood pressure groups.

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Table 7. Adjusted comparisson for arterial parameters between normal and high pressure groups.

	NBP (n = 577)	HBP (n = 239)	*p* value NBP vs. HBP
A) Adjusted by age, body height and weight			
Tonometry at radial artery (SphygmoCor)			
Pf_{SCOR} (mmHg)	32 ± 1	37 ± 1	**0.000**
Pb_{SCOR} (mmHg)	13 ± 1	14 ± 1	**0.000**
Reflection Index Ratio (Pb_{SCOR}/Pf_{SCOR})	0.42 ± 0.01	0.41 ± 0.01	0.457
$AIx@75_{SCOR}$	0.50 ± 0.39	0.00 ± 0.65	0.529
Oscillometry at brachial artery (Mobil-O-Graph)			
Pf_{MOG} (mmHg)	25 ± 1	28 ± 1	**0.000**
Pb_{MOG} (mmHg)	14 ± 1	15 ± 1	**0.034**
Reflection Index Ratio (Pb_{MOG}/Pf_{MOG})	0.57 ± 0.01	0.56 ± 0.01	0.059
$AIx@75_{MOG}$	13.2 ± 0.41	15.8 ± 0.71	**0.002**
B) Adjusted by age, body height and weight, HR, CO and SVR			
Tonometry at radial artery (SphygmoCor)			
Pf_{SCOR} (mmHg)	33 ± 1	38 ± 1	**0.000**
Pb_{SCOR} (mmHg)	13 ± 1	15 ± 1	**0.000**
Reflection Index Ratio (Pb_{SCOR}/Pf_{SCOR})	0.42 ± 0.01	0.40 ± 0.01	0.073
$AIx@75_{SCOR}$	-0.25 ± 0.46	-2.26 ± 0.81	**0.044**
Oscillometry at brachial artery (Mobil-O-Graph)			
Pf_{MOG} (mmHg)	25 ± 0.3	28 ± 1	**0.000**
Pb_{MOG} (mmHg)	14 ± 0.2	16 ± 0.4	**0.000**
Reflection Index Ratio (Pb_{MOG}/Pf_{MOG})	0.57 ± 0.01	0.56 ± 0.01	**0.043**
$AIx@75_{MOG}$	14.1 ± 0.3	13.4 ± 0.5	0.292
C) Adjusted by age, body height and weight, HR, CO, SVR, pSBP, pPP and arterial stiffness levels			
Tonometry at radial artery (SphygmoCor)			
Pf_{SCOR} (mmHg)	31 ± 1	32 ± 1	0.397
Pb_{SCOR} (mmHg)	13 ± 1	13 ± 1	0.603
Reflection Index Ratio (Pb_{SCOR}/Pf_{SCOR})	0.42 ± 0.01	0.42 ± 0.01	0.915
$AIx@75_{SCOR}$	2.73 ± 0.54	1.94 ± 0.82	0.462
Oscillometry at brachial artery (Mobil-O-Graph)			
Pf_{MOG} (mmHg)	24 ± 1	25 ± 1	0.26
Pb_{MOG} (mmHg)	13 ± 1	14 ± 1	0.47
Reflection Index Ratio (Pb_{MOG}/Pf_{MOG})	0.56 ± 0.01	0.55 ± 0.01	0.37
$AIx@75_{MOG}$	15.51 ± 0.61	16.66 ± 0.87	0.33

Values expressed as mean value (MV) ± standard deviaton (SD). SVR: systemic vascular resistances. PWV: pulse wave velocity. CIMT: carotid intima-media thickness. AD: arterial cross-sectional distensibility. CCA and CFA: common carotid and femoral artery, respectively. Pf and Pb: amplitude of forward and backward components of aortic wave. AIx@75: aortic augmentation index normalizd for a heart rate of 75 beats/minute. SCOR and MOG indicate parameters obtained with the SphygmoCor and Mobil-O-Graph devices. NBP and HBP normotensive and high blood pressure groups, respectively. A $p < 0.05$ was accepted as statistically significant.

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explanatory factors and their potential variations and role in HBP states.

The Work Main Findings Were

• First, when data (Pf, Pb, Pb/Pf and AIx) from SphygmoCor and Mobil-O-Graph, two main systems used to determine wave components and reflection parameters were compared, both systematic and proportional errors were identified [Table **2**].

SCOR capability to assess cBP in adults has been evaluated and demonstrated in several works, but data related with the system capability to assess cBP in children and adolescents is limited.

Recently, Milne *et al*. (2016) compared SCOR data with information obtained from carotid wall tracking (ART.LAB system), which had been previously compared to data directly measured in the aortic root during arterial cannulation [21]. The authors concluded that SCOR could be used to assess cBP in children. In turn, Weiss *et al*. (2012) demonstrated that cBP could be adequately estimated by non-invasive oscillometry (MOG), which would have the advantage of measuring brachial pBP and providing cBP within a single recording (internal self-calibration) [22]. Central BP reference values for children and adolescents have been recently defined using MOG data [23].

As stated above, SCOR and MOG would be of value in assessing cBP. In this work we used both systems and analyzed comparatively data obtained with them. In our population, Pf, Pb, Pb/Pf and AIx data obtained with SCOR and MOG showed not only differences in absolute values (systematic or mean error), but also differences associated with the parameters mean values (proportional error) [Table **2**]. Thus, aortic wave data obtained with MOG and SCOR cannot be used interchangeably. SCOR and MOG systems differ in the methods used to obtain the aortic wave and in the physical-mathematical approaches considered for PWA and WSA. Those differences could contribute to explain the results obtained when assessing the agreement between systems. Further studies would be necessary to explain the differences between data obtained with SCOR and MOG, to analyze their meaning and the potential usefulness of developing a SCOR-to-MOG (or viceversa) conversion factor.

• Second, in children and adolescents both, Pf and Pb were positively associated with male sex, age, body height, weight and BMI. In turn, Pb/Pf ratio increased in association with increases in body weight. AIx@75 was positively associated with female sex; at the time it showed a negatively association with body height, weight and BMI [Table **3**].

In children and adolescents, cBP levels increase with age [14, 23, 24] and body height [23], being the rate of change higher in males [14] and during hypertensive conditions [24]. Looking at our findings it could be said that ageing-related increases in cBP would be explained by increases in both Pf and Pb. The higher rate of cBP increase observed in males could be associated with their faster growth in height [Table **3**]. The increase in cSBP (and in pSBP) observed in association with body weight increase [25] could be explained by a rise in Pf and Pb. Body weight increases would associate increases in Pb/Pf ratio. Thus, the higher the body weight, the higher the peripheral reflection coefficient. Jointly analyzing the associations between wave components and anthropometric data it could be said that the older the subject and the higher his weight, the higher the pressure load. That would be particularly true in males.

Our findings related with AIx@75 are in agreement with those observed in adults [1]. The shortest heights associate an earlier arrival of reflected waves, which could be explained by a greater proximity of reflection sites (*i.e.* bifurcations, tapers) [1]. That contributes to explain the higher AIx@75 observed in females, who are shorter than males [26-28]. Another possible mechanism may be the smaller radius of the abdominal aorta in girls compared to boys of same body size. About this, PWV increases in aorta with smaller radius according to Moens–Korteweg equation that describes the relation between PWV and the radius of tube (artery). Other factors would also contribute to explain the greater AIx in females since in children matched for age, body size and/or cardiorespiratory fitness there were no significant differences in HR or cBP between girls and boys, but girls showed greater AIx [14, 29].

The combination of lower Pb and higher AIx would result somewhat paradoxical if Pb and AIx determinants are unknown. Pb (but not AIx) depends on Pf, which in turn is determined by the ejection volume and the aortic impedance. The greater Pf, the greater Pb. AIx depends on the distance from reflection sites to ascending aorta. Shorter distances result in earlier Pb arrivals. The lower Pf levels observed in females would contribute to their lower Pb, while the reduced path lengths between the reflection sites and the aorta would result in earlier arrival of the reflections and greater AIx. Another factor to analyze is arterial stiffness' effects. An increase in arterial stiffness results in an increased velocity of propagation and in reduced attenuation of wave propagation. Then, increases in AIx and Pb (as well as in Pf) would be expected in association with a rise in arterial stiffness. Considering the stated above, it could be said that Pb and AIx give complementary information related with the reflections contribution to cPP, and although they are frequently modified in a similar way, sometimes they are not, particularly in childhood.

The Pb/Pf ratio (but not AIx), an index of the reflection magnitude has the advantage of being HR-independent as it does not dependent on the inflection point timing [2]. Females showed lower Pb and Pb/Pf, but due to the earlier arrival of reflections, reflected waves contribution to cBP would be greater, being AIx@75 higher in females.

• Third, higher Pf and Pb levels were observed in association with higher pSBP, pMBP, pPP and cardiac output, and in association with reduced pDBP, HR and SVR levels. Pb/Pf ratio was positively associated with HR, SVR, pSBP, pDBP and pPP. AIx@75 was negatively associated with pSBP, pPP and cardiac output and positively associated with pDBP, HR and SVR [Table **4**].

Pf and Pb determine, at the same time they are determined by BP levels. About this, Pf and Pb integration determines cBP which due to passive distension would determine arterial stiff-

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ness and thus Pf and Pb. Then, the positive association of Pf and/or Pb with SBP and/or PP levels was expected. An increased stroke volume (cardiac output) results in increased Pf, followed by an increase in Pb (disregard of arterial stiffness levels). Reduced SVR associate reduced DBP levels and wave reflections [1], which is in agreement with our finding of a negative association between SVR and both, Pf and Pb. Low HR levels associated reduced viscoelasticity (stiffness) and BP levels [30], which could contribute to explain the low Pf and Pb levels observed in association with reduced HR. The association between higher Pb/Pf levels and HR, SVR, pSBP, pDBP and

pPP levels could be understood taking into account a higher contribution of reflections are expected in association with conditions with higher arterial stiffness, BP and SVR.

The highest AIx levels were found in association with the lowest SBP. That could be initially considered paradoxical, but it would be explained considering subjects age (range: 3-20 years). The youngest subjects showed the lowest body height, and consequently the highest AIx, at the time their HR levels were the highest and their SBP levels the lowest.

- Fourth, Pf and Pb were positively associated with local and regional arterial stiffness (cfPWV and AD), PWV ratio and CIMT. Opposite findings were observed for AIx@75 [Table **4**].

Jointly analyzing the findings described above it could be said that even at early ages high BP components associate higher stiffness (carotid, femoral and aortic) and wall thickness levels. The associations between AIx and arterial properties could be understood taking into account subjects' height. This highlights height's meaning as an AIx determinant and suggests AIx variations or differences in children and adolescents would not have the same meaning or explanations given in adults. In this context, the use of reflection indexes standardized or adjusted for body size would be of value.

- Fifth, HR, pPP, height and weight were the variables that in isolation (simple associations) or combined (multiple associations), showed the major capability to explain the interindividual differences in Pf, Pb, Pb/Pf and AIx. Arterial stiffness also showed explanatory capability, being the carotid the artery with major contribution. In children, once height and weight are known, the knowledge of the subject's age is not necessary to determine the expected Pf, Pb, Pb/Pf ratio or AIx levels.

The pPP and HR (hemodynamic variables obtained in routine clinical practice) explained ~50% (SCOR) and ~40% (MOG) of Pf interindividual variations (Model1). Demographic-anthropometric (Model 2) and arterial (Model 3) data showed a limited contribution to explain interindividual variations in Pf [Table **5**]. Anyway, both height and weight contributed significantly to Model 2. Among the arterial properties considered (Model 3), carotid stiffness showed the strongest association with Pf. That could be explained taking into account the carotid, as a "central" artery would represent the ascendant aorta stiffness better than thoracic-abdominal vessels. Multivariate models (Model 4 and 5), increased the capability to explain Pf variations (~62% with Model 5, for SCOR data).

Peripheral PP and weight were variables common to Pf to the explanatory equations obtained for SCOR and MOG [Table **5**]. For SCOR-derived data, age, body weight and height, pPP, HR and CCA AD explained ~62% of Pf variations. If only pPP, weight and carotid stiffness were known, ~60% of Pf variations would be explained [Table **5**]. Thus, considering other variables would not increase significantly the explanatory capability.

Disregard of the system considered (SCOR or MOG), ~40-45% of Pb variations were explained by pPP and HR. In turn, anthropometric-demographic (Model 2) and arterial (Model 3) variables only explained ~10-20% of Pb variations. Body height and weight, rather than age would explain Pb variations. Carotid stiffness rather than thoracic-abdominal aorta stiffness contributed to explain Pb (Model 3).

Unlike that described for Pf, variables integration (Model 4 and 5), did not significantly improve the explanatory capability obtained with pPP and HR [Table **5**]. In general terms, when considering similar independent variables, the obtained models explained Pf variations better than variations in Pb [Table **5**].

Peripheral hemodynamic variables contributed to explain ~17-21% of Pb/Pf variations (Model 1). When SCOR data were considered anthropometric-demographic variables allowed explaining ~17% of Pb/Pf variations (Model 2). When variables from different categories were integrated in a single model (Models 4 and 5), ~24-35% of the variations in Pb/Pf were explained, being body height and HR the explanatory variables in common between MOG and SCOR data [Table **5**]. Greater the body height then, lower Pb/Pf ratio, which could be explained by the larger Pb attenuation as it "travels" over a greater length. On the other hand, higher the HR then, lower Pb/Pf ratio. This could be associated with a reduced systolic volume and BP (lower Pf and Pb), and with a greater viscoelastic attenuation of travelling waves, which would mainly impact Pb (rather than Pf).

Hemodynamic variables allowed explaining ~26% (SCOR) and ~40% (MOG) of the variations in AIx@75, being pPP and HR the explanatory variables in common between both systems. Disregarding the system considered, age and body height were the significant anthropometric-demographic variables capable of explaining AIx@75 variations.

When the different variables from different categories were integrated the capability to explain AIx@75 variations increased, with differences depending on the system used (SCOR o MOG). Height and HR were significant explanatory variables (Model 5), disregard of data origin [Table **5**].

- Sixth, HBP states associated higher Pf, Pb, AIx and lower Pb/Pf ratio [Table **6**]. Those findings were observed, together with higher weight, arterial stiffness and HR.

It could be said HBP states associate vascular and hemodynamic (*i.e.* increased HR and carotid stiffness levels) changes that could be identified even at early ages [Table **6**]. In addition, higher body weight levels were observed in association with HBP. This is in agreement with the proposal that HBP and other cardiovascular risk factors tend to cluster. Particularly, HBP states during childhood have shown to

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be associated with overweight and/or obesity [31]. Taking into account the positive association between body weight and wave components (Pf and Pb) it could be proposed, at least in theory, that higher weight levels could explain differences in wave components [Tables **4** and **5**]. However, the HBP group showed higher Pf and Pb even after adjusting for anthropometric and demographic variables. Thus, age or body complexion would not be enough to explain the higher Pb and Pf levels observed in association with HBP states in children and adolescents. HR and global hemodynamic conditions would contribute to explain BP wave components characteristics during HBP states. Increased SVR observed in association with HBP states would result in higher mean BP levels, associated with increased Pf (and hence Pb) and reflections (that also contribute increase Pb) [1]. However, after adjusting for HR, CO and SVR, subjects from the HBP group showed greater Pf and Pb levels. Then, the wave components (Pf and Pb) characteristics associated with HBP states would not be explained by anthropometric-demographic or hemodynamic factors.

Compared to children and adolescents with normotensive BP levels, those with HBP showed higher carotid stiffness. In turn, at least in theory increased carotid stiffness would contribute to explain the greater Pb and Pf levels observed in HBP states. On the contrary, normotensive and HBP subjects did not show significant differences in femoral (CFA AD), thoracic-abdominal aorta (carotid-femoral PWV) nor in upper limb (carotid-radial PWV) stiffness. Thus, in early stages of life (childhood) the vascular changes associated with HBP would be observed in central rather than in peripheral arteries. So, if we are looking for an early marker of hypertensive vascular damage in childhood, carotid stiffness would show advantages over other arteries and stiffness indexes.

Finally, when pBP and arterial stiffness levels were considered, normotensive and HBP subjects did not show differences in Pb and Pf. Then, vascular properties, like arterial stiffness, contribute to explain the differences in Pb and Pf between normotensive and HBP subjects (at the time BP determines arterial properties). Jointly analyzing our findings it could be said that the greater Pb and Pf levels observed in HBP states, would have several explanatory factors: anthropometric (*i.e.* increased weight), hemodynamic (*i.e.* increased HR) and arterial (*i.e.* increased carotid stiffness). Only controlling for all those factors the differences in wave components between normotensive and HBP subjects would disappear.

4.1. Clinical Implications: Equipment-related Discrepancies in Wave Parameters in Children and Adolescents

SCOR and MOG systems give similar parameters from cBP wave, considering different methodological approaches. Advantages and limitations have been described for both systems. Limitations ascribed to applanation tonometry (SCOR) are: 1) difficulties to obtain high-quality waves (*i.e.* obese subjects, subjects with low BP and/or with a radial pulse difficult to be identified), 2) operator dependency and 3) radial wave calibration using mean (or systolic) and diastolic pressure levels obtained in a proximal (brachial) site [2].

MOG uses a conventional brachial cuff to measure pSBP and pDBP. Then it uses a volumetric displacement signal inflating the cuff to a sub-diastolic pressure level. It has been proposed that some limitations ascribed to SCOR would be overcame using MOG system. About that, it would be useful even in subjects with low BP or with a hard to palpate pulse. In addition the method is operator independent [2].

Finally, MOG involves self-calibration, since BP signal is calibrated with the measured brachial BP. At the time, there is a tendency to employ cuff-based acquisition systems (*i.e.* SphygmoCor XCEL development) considering the ease of use in clinical practice; the advantages of tonometry are recognized. About this, data acquisition frequencies are higher than those obtained by cuff volumetric displacement, which dampens higher-frequency information [2]. Thus, tonometry would be particularly advantageous when high-frequency components are of interest (*i.e.* AIx determination).

SCOR and MOG data have shown correspondence and equivalence in their capability to determine pBP and cBP. However, when data obtained by means of PWA and WSA were considered, the systems showed both systematic and proportional differences. Then, it is clear that in children and adolescents SCOR and MOG data could not be used interchangeably, as was described and explained previously [2].

4.2. Clinical Implications: Physiological and Pathophysiological Aspects

We found that in children and adolescents, HR, pPP, weight, height and central arteries stiffness are among the main determinants of wave reflection (in absolute – Pb - and relative –Pb/Pf, AIx- terms). Then, changes in those explanatory variables during growth and development would result in cBP variations (due changes in wave Pf and Pb components, reflections levels and time of arrival). In other words, deviations from the expected anthropometric or hemodynamic conditions would result in cBP deviations. Our findings highlight the importance of the knowledge and understanding of the explanatory variables for an adequate interpretation of BP levels and wave-derived data.

4.3. Limitations

Up to now, there is no gold standard technique to determine pulse wave components and derived parameters. Then, we opted for using two validated systems approved for use in both clinical and research fields. The use of the pressure-blood flow ‘‘triangulation method’’ of aortic wave separation to derive aortic Pf and Pb has been largely employed and shown adequate reproducibility and clinical value. Tade *et al*. showed similar relations between Pf or Pb and cardiovascular remodeling when Pb or Pf was derived from WSA employing pressure and blood flow measurements versus Pb or Pf derived from the triangular waveform approach to WSA [32]. Our work has the limitation of being a cross-sectional design. Therefore, we could not determine the temporal profile of our findings and/or whether there would be a “cumulative” effect of the hemodynamic conditions and changes. Third, we opted for working with a healthy popula-

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tion, taking into account we aimed at evaluating the physiological association between aortic wave components and several potential demographic, anthropometric and arterial determinants, considering vessels non-exposed to drugs and without cardiovascular disease. Thus, our population was similar to those described or considered to define reference intervals [23]. The obtained results could be "modified" in other contexts (*i.e.* cardiovascular disease) which would require further studies. Additionally, it should be noted that although we have shown that in children and adolescents some cardiovascular risk factors may be associated with wave components and reflections indexes (*i.e*. smoking and Pb_{SCOR}) (Table **3**), in the present work we did not go deeply into the analysis of those associations and risk factors were not included in the multivariate analyzes.

CONCLUSION

HR, pPP, body height and weight were the variables that in isolation (simple associations) or combined (multiple associations), showed the major capability to explain the inter-individual differences in Pf, Pb, Pb/Pf and AIx. Arterial stiffness, mainly carotid stiffness also showed explanatory capability. Once body height and weight are known, the knowledge of the subject age is not necessary to determine the expected Pf, Pb, Pb/Pf ratio or AIx levels.

HBP states were associated with higher Pf, Pb, AIx and with a lower Pb/Pf ratio. Covariate analysis enable showing that wave components (Pf, Pb) characteristics associated with HBP states would not be explained by anthropometric-demographic or hemodynamic factors.

SphygmoCor and Mobil-O-Graph systems did not give similar wave derived parameters, but there were both systematic and proportional differences between data obtained with the referred devices.

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 or their guardians.

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) and Espacio Interdisciplinario (EI) and Comisión Sectorial de Investigación Científica (CSIC-Udelar) of the Republic University, Uruguay. Additionally, this work was supported by extra-budgetary 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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