

## Impaired Central Pulsatile Hemodynamics in Children and Adolescents With Marfan Syndrome

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**Background**—Marfan syndrome is characterized by aortic root dilation, beginning in childhood. Data about aortic pulsatile hemodynamics and stiffness in pediatric age are currently lacking.

**Methods and Results**—In 51 young patients with Marfan syndrome ( $12.0 \pm 3.3$  years), carotid tonometry was performed for the measurement of central pulse pressure, pulse pressure amplification, and aortic stiffness (carotid-femoral pulse wave velocity). Patients underwent an echocardiogram at baseline and at 1 year follow-up and a genetic evaluation. Pathogenetic fibrillin-1 mutations were classified between “dominant negative” and “haploinsufficient.” The hemodynamic parameters of patients were compared with those of 80 sex, age, blood pressure, and heart-rate matched controls. Central pulse pressure was significantly higher ( $38.3 \pm 12.3$  versus  $33.6 \pm 7.8$  mm Hg;  $P=0.009$ ), and pulse pressure amplification was significantly reduced in Marfan than controls ( $17.9 \pm 15.3\%$  versus  $32.3 \pm 17.4\%$ ;  $P<0.0001$ ). Pulse wave velocity was not significantly different between Marfan and controls ( $4.98 \pm 1.00$  versus  $4.75 \pm 0.67$  m/s). In the Marfan group, central pulse pressure and pulse pressure amplification were independently associated with aortic diameter at the sinuses of Valsalva (respectively,  $\beta=0.371$ ,  $P=0.010$ ;  $\beta=-0.271$ ,  $P=0.026$ ). No significant difference in hemodynamic parameters was found according to fibrillin-1 genotype. Patients who increased aortic Z-scores at 1-year follow-up presented a higher central pulse pressure than the remaining ( $42.7 \pm 14.2$  versus  $32.3 \pm 5.9$  mm Hg;  $P=0.004$ ).

**Conclusions**—Central pulse pressure and pulse pressure amplification were impaired in pediatric Marfan syndrome, and associated with aortic root diameters, whereas aortic pulse wave velocity was similar to that of a general pediatric population. An increased central pulse pressure was present among patients whose aortic dilatation worsened at 1-year follow-up. (*J Am Heart Assoc.* 2017;6:e006815. DOI: 10.1161/JAHA.117.006815.)

**Key Words:** arterial stiffness • blood pressure • central blood pressure • children • fibrillin-1 • Marfan syndrome

requently, Marfan syndrome (MFS) is not diagnosed until adolescence or adulthood. However, with improved understanding of the value of an early diagnosis, an increasing number of children in whom MFS is suspected are referred for assessment. Cardiovascular abnormalities are often asymptomatic, and a careful cardiovascular evaluation is essential for both diagnosis and follow-up of cardiovascular complications. Unfortunately, only a few studies focused specifically on

pediatric age, and a strategy to clearly identify the risk profile by means of genetic or imaging assessment is not available.

Currently, the detection of initial aortic root enlargement, probably the best indicator of dissection risk and hence of the need for prophylactic replacement, is an important way to early diagnosis of a potentially fatal complication.<sup>1</sup> Although the incidence of aortic dissection is age dependent and rare in children and adolescents,<sup>2,3</sup> an initial aortic root dilatation can

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## Clinical Perspective

### What Is New?

- Central pulse pressure and pulse pressure amplification are impaired in pediatric patients with Marfan syndrome and are associated with aortic root diameter, the only validated indicator of aortic dissection risk.
- An increased central pulse pressure is present among patients whose aortic dilatation worsened at 1-year follow-up.

### What Are the Clinical Implications?

- Central blood pressure parameters, such as central pulse pressure and pressure amplification, are able to identify very early hemodynamic abnormalities in pediatric Marfan syndrome patients.
- Evaluation of central pulse pressure may increase the prediction of progressive aortic dilatation in pediatric Marfan syndrome patients, although further studies are required to confirm our findings.

be observed even in early ages, already requiring prophylactic changes in children and adolescents' lifestyle, while becoming clinically more relevant in adults.<sup>4</sup> Recent developments in the aortic dissection risk assessment by genotyping of fibrillin-1 (FBN1) are promising, but currently validated only in an adult cohort.<sup>5</sup> In this context, however, a strategy for an early diagnosis of cardiovascular involvement is necessary to improve outcomes in later age.

Control of blood pressure (BP) values with antihypertensive medications is currently the main approach to significantly affect the long-term outcomes of pediatric MFS. Beta-blockers and renin-angiotensin-aldosterone system antagonists are known to slow the rate of progression of aortic dilatation in children and young adults with MFS,<sup>6</sup> confirming the relevant role of BP control in the treatment of aortic complications of MFS. In recent years, central BP assessment has demonstrated the potential for a widespread clinical use and may provide additional information about vascular phenotype, especially in children and adolescents.<sup>7</sup> Central pulse pressure (cPP), which is the difference between the systolic and diastolic BP in the proximal aorta, is emerging as a major determinant of aortic remodeling.<sup>8,9</sup> In a small study of 20 adult patients with MFS, cPP was a major determinant of ascending aorta diameter, whereas brachial pulse pressure was not.<sup>10</sup> Indeed, central BP levels and the amplification of BP values along the arterial tree are strictly associated with the stiffening of large arteries and with the timing of reflected waves.<sup>11</sup> Arterial stiffness is known to be altered in adult patients with MFS,<sup>12</sup> but evidence in pediatric age is limited.<sup>13–15</sup> Aortic stiffness can be accurately and easily

measured as carotid-femoral pulse wave velocity (PWV) with arterial tonometry, a recommended method also for measuring central BP values.<sup>16</sup>

The aim of this study is to evaluate central pulse wave analysis variables and arterial stiffness, measured with arterial tonometry, in a cohort of children and adolescents affected by MFS, compared with a control group of healthy individuals. We then considered the association of these hemodynamic parameters with the diameters of the ascending aorta measured with echocardiography at baseline and at the 1-year follow-up and with the FBN1 genotype.

## Methods

### Study Cohort

Fifty-one consecutive pediatric MFS patients were recruited among the patients regularly followed in a reference center for MFS (Marfan Clinic, Sacco Hospital, Milan, Italy), from March 2014 to April 2015. Diagnosis of MFS was established according to revised Ghent criteria.<sup>17</sup> Exclusion criteria were: age less than 5 or more than 18 years; history of aortic surgery; aortic dissection; or aortic aneurysm distal to aortic root. Patients underwent a clinical and dysmorphological evaluation, transthoracic echocardiography, and arterial tonometry in the same day. Anthropometric parameters and clinical history were collected during the clinic visit. The study protocol was approved by the local ethics committee and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained, depending on age, from patients or their parents or legal representatives, before enrollment in the study.

### Control Group

Control group was selected from a large database of individuals undergoing applanation tonometry recordings in the frame of a general population study.<sup>18</sup> Control subjects who were receiving any cardiovascular drug were excluded. Eighty control subjects were selected to match Marfan population for age, mean arterial pressure, heart rate, and sex. Z-scores for height and body mass index (BMI) were calculated for both Marfan and control groups, using the National Health and Nutrition Survey, Centers for Disease Control and Prevention/National Center for Health Statistics charts.

### Echocardiography

A complete echocardiographic study was performed in the MFS population with a full ultrasound system (Philips EnVisor C-HD; Philips Co, Best, The Netherlands) at baseline and at the 1-year follow-up. Aortic root diameters were measured

according to current guidelines.<sup>19</sup> Aortic measurements were obtained in the parasternal long-axis view. The measurements were taken at the aortic valve “annulus” at the hinge points of the leaflets, aortic root at the largest diameter within the sinuses of Valsalva, sinotubular junction at the transition point from sinus to tubular aorta, and ascending aorta at the level of the right pulmonary artery. All echocardiographic images were acquired and recorded digitally and analyzed by a single observer, blinded to the clinical conditions of patients. Aortic Z-score was calculated with the Colan formula,<sup>20</sup> according to recommendations of the Marfan Foundation. Aortic Z-score with correction for body height was used in the regression analysis because of its best clinical performance.<sup>21</sup> Aortic dilatation was defined according to Ghent 2010 criteria for patients aged <20 years.<sup>17</sup>

### Arterial Functional Parameters

Central BP values and aortic pressure waveforms were obtained directly from the common carotid artery using an applanation tonometer.<sup>22,23</sup> A validated, easy-to-use, and high-fidelity PulsePen tonometer (DiaTecne srl, Milan, Italy) was used. This device has been previously described in detail.<sup>22</sup> As previously demonstrated, pressure waves recorded noninvasively by the PulsePen tonometer at the site of the common carotid artery are similar to pressure waveforms obtained invasively by means of an intra-arterial catheter.<sup>22</sup> Moreover, several studies demonstrated that central BP values and pulsed wave analysis recorded in the common carotid artery are a reliable surrogate of analysis recorded in the aorta by invasive methods.<sup>11,24,25</sup> Central BP values were obtained by the carotid BP curve integral after calibration with brachial mean and diastolic BP measured noninvasively by a validated oscillometric sphygmomanometer at the brachial artery (Omron 705IT; Omron Co, Kyoto, Japan). The pulse pressure amplification (PPA) was the percentage of increase of pulse pressure in the brachial artery relative to cPP, according to the formula:  $PPA = 100 \times (PP \text{ in the brachial artery} - cPP) / cPP$ . The augmentation index was defined as the difference between the second and first systolic peaks and expressed as a percentage of cPP.<sup>11</sup> Because Alx is affected by heart rate, Alx values were normalized for a theoretical heart rate of 75 bpm ( $Alx_{@75}$ ) by a conventional formula.<sup>26</sup>

The PulsePen device was also used for measuring carotid-femoral PWV, which is considered the gold standard for measuring aortic stiffness.<sup>27</sup> The procedure has been described in detail previously.<sup>22</sup> Briefly, the PulsePen consists of a tonometer and an integrated ECG unit. PWV is measured by sequential recordings of the arterial pressure waveform at the common carotid and femoral artery and calculated as the distance between the sampling sites divided by the time

difference between the respective delays in the onset of femoral and carotid pulses with regard to the preceding R wave of an ECG recording. The distance traveled by the pulse waveform from heart to femoral artery site is thus approximately estimated as 80% of the direct carotid-to-femoral tape measure distance, as recommended by a recent expert consensus document on the measurement of aortic stiffness in daily practice.<sup>28</sup> All the variables derived from arterial tonometry assessment were obtained through the proprietary PulsePen software, which automatically analyzed recorded pulse waveforms and provided central BP values. All recordings were performed by 2 qualified operators (A.G. and P.S.) who were blinded to the diagnosis made in the subjects under evaluation. The use of the PulsePen device in children was validated in a previous study, which provided reference values for carotid-femoral PWV in children and adolescents.<sup>18</sup> In that study, the intra- and interobserver coefficients of variation of PWV measurements were 5.7% and 6.1%, respectively.

### Genetics

Genetic analysis was performed at the Department of Molecular Genetics of the Istituto Auxologico Italiano (Milan, Italy). Mutation screening, with the consent of the patient or a guardian, was performed on genomic DNA extracted from peripheral blood cells using a commercial kit (Puregene Blood Core Kit B; Qiagen, Minneapolis, MN), following manufacturer instructions. The entire coding region of the FBN1 gene was screened by direct sequencing. Polymerase chain reaction fragments were sequenced using the BigDye Terminator Kit (Applied Biosystems, Foster City, CA) and analyzed on the ABI Prism 3500 automated sequencer (Applied Biosystems). According to the international database UMD-FBN1<sup>29</sup> and Alamut software (Interactive Biosoftware, Rouen, France), mutations were classified as: previously described mutation; not previously described mutation; surely disease-causing mutation; probably disease-causing mutation; or DNA variation of uncertain significance. Mutations were also categorized according to the exon of place in the FBN1 gene (1–64) and depending on the type of mutation (missense, nonsense, frameshift, and splicing). Moreover, effects of mutations were predicted by Alamut software, to classify pathogenetic FBN1 mutations as “haploinsufficient” or “dominant negative.” This approach was validated in a previous study.<sup>30</sup> Mutations were also listed as familiar or “de novo.”

### Statistical Analysis

Qualitative variables are expressed in percentage, continuous variables as mean  $\pm$  SD, or confidence interval 95%. Qualitative data were compared with Pearson’s chi-square or Fisher’s exact test, when appropriated, and continuous variables with

a *t* test. Continuous variables were tested to detect substantial deviations from normality by computing the Kolmogorov–Smirnov *Z*; homoscedasticity was detected using Levene's test. The assumption of satisfactory normal distribution was met for all the examined variables. Continuous variables were correlated with simple or multiple linear regression. Degree of correlation is expressed as Pearson's *R*.

Linear regression models were constructed using important covariates to elucidate independent determinants of aortic diameters. Variance inflation factor was computed to check multicollinearity between independent variables in linear regression models, with a cut-off value of 5. In the regression models, anthropometric (age, sex, and BMI Z-scores) and hemodynamic variables (mean arterial pressure, heart rate) were considered as explanatory variables of aortic diameters, together with the hemodynamic measurements. Left ventricular ejection time was preferred to heart rate when measures of PWV were inserted in the models, because of the closer relationship of ventricular ejection time with PWV reported in previous studies.<sup>31</sup> Receiver operating characteristic curve analyses were calculated to assess the diagnostic power of the examined variables, and the area under receiver operating characteristic curve (AUC) was provided. Differences were defined as significant in the presence of  $P < 0.05$ . Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, Release 20.0; SPSS, Inc, Chicago, IL).

## Results

### Comparison Between Marfan and Control Populations

The descriptive anthropometric, clinical, and echocardiographic characteristics of the study population are shown in Table 1. With regard to therapy, 64.7% of the patients were in therapy with Losartan (dosage per kg,  $1.16 \pm 0.40$  mg/kg; duration of therapy,  $4.55 \pm 2.00$  years), whereas 13.7% were in therapy with Atenolol (dosage per kg,  $0.66 \pm 0.33$  mg/kg; duration of therapy,  $3.91 \pm 1.67$  years). A comparison between MFS patients and controls was made for the main hemodynamic variables derived from arterial applanation tonometry (Figure 1). MFS showed an increased cPP compared with controls ( $38.3 \pm 12.3$  versus  $33.6 \pm 7.8$  mm Hg;  $P = 0.009$ ), whereas peripheral pulse pressure was not significantly different (Table 1). A reduced PPA was present in the comparison with controls ( $17.9 \pm 15.3\%$  versus  $32.3 \pm 17.4\%$ ;  $P < 0.0001$ ). PWV was not significantly different from controls ( $4.98 \pm 1.00$  versus  $4.75 \pm 0.67$  m/s;  $P = 0.12$ ).

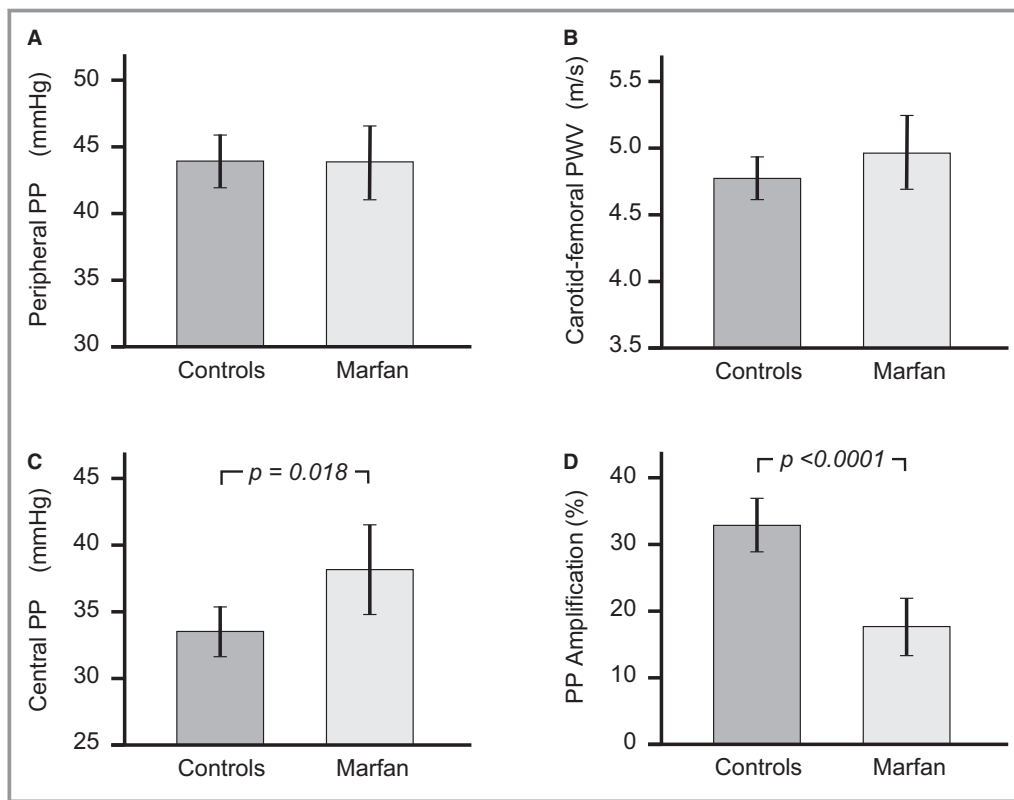
We analyzed the direct correlations of the examined hemodynamic parameters with height and BMI Z-scores. In the MFS population, PPA and PWV were not significantly

**Table 1.** General Characteristics of Marfan Patients, According to the Presence of Aortic Dilatation

Parameters	Marfan (n=51)	Controls (n=80)	P Value
<b>General characteristics</b>			
Sex (males/females)	29/22	45/35	0.95
Age, y	$12.0 \pm 3.3$	$11.9 \pm 2.4$	0.90
BMI Z-score	$-0.71 \pm 1.56$	$-0.27 \pm 0.98$	0.05
Height Z-score	$2.09 \pm 1.38$	$0.44 \pm 0.81$	$< 0.0001$
Mean arterial pressure, mm Hg	$70.7 \pm 7.9$	$71.0 \pm 3.9$	0.72
Peripheral pulse pressure, mm Hg	$43.9 \pm 10.2$	$43.6 \pm 8.2$	0.88
Heart rate, bpm	$73.2 \pm 15.7$	$74.6 \pm 8.40$	0.51
<b>Ghent criteria</b>			
Aortic dilatation	43 (84.3%)	...	...
Ectopia lentis	32 (62.7%)	...	...
Family history	35 (68.6%)	...	...
FBN1 mutation	40 (78.4%)	...	...
Systemic score $\geq 7$	43 (84.6%)	...	...
Total score	$8.8 \pm 2.8$	...	...
<b>Therapy</b>			
Angiotensin II receptor blocker	33 (64.7%)	...	...
Beta-blocker	7 (13.7%)	...	...
<b>Echocardiographic measurements</b>			
Aortic valve annulus, mm	$19.8 \pm 2.5$	...	...
Aortic diameter Sinuses of Valsalva, mm	$31.8 \pm 4.7$	...	...
Aortic diameter ST junction, mm	$24.2 \pm 4.1$	...	...
Aortic diameter ascending aorta, mm	$24.7 \pm 3.9$	...	...
Aortic Z-score	$1.81 \pm 1.16$	...	...
Aortic Z-score $\geq 2$	23 (45.1%)	...	...
Aortic Z-score $\geq 3$	10 (19.6%)	...	...
Mitral valve prolapse	44 (86.2%)	...	...
Aortic regurgitation	2 (3.9%)	...	...
Ejection fraction, %	$63.2 \pm 3.1$	...	...

Data are reported as mean  $\pm$  SD or percentage. BMI indicates body mass index; BSA, body surface area; FBN1, fibrillin-1.

related either with BMI Z-score (PPA,  $R = -0.027$ ,  $P = 0.849$ ; PWV,  $R = 0.117$ ,  $P = 0.407$ ) or with height Z-score (PPA,  $R = -0.151$ ,  $P = 0.287$ ; PWV,  $R = 0.143$ ,  $P = 0.312$ ). cPP was not related to BMI ( $R = 0.265$ ;  $P = 0.058$ ), but had a borderline significant correlation with height Z-score ( $R = 0.295$ ;



**Figure 1.** Hemodynamic parameters in Marfan and control groups: peripheral pulse pressure (A); carotid-femoral pulse wave velocity (B); central pulse pressure (C); pulse pressure amplification (D). Means±confidence intervals 95%. PP indicates pulse pressure; PWV, pulse wave velocity.

$P=0.034$ ). In the control group, there was no significant correlation among BMI or height Z-scores and hemodynamic parameters (cPP, PPA, and PWV).

We have also analyzed arterial wall properties in the MFS population according to sex. Male MFS patients ( $n=29$ ) showed a significantly higher cPP than females ( $n=22$ ; Table 2), despite similar anthropometric characteristics and BP values, but did not show significantly different PPA and PWV values.

### Correlation of Hemodynamic Variables With Aortic Echocardiographic Measurements

In the MFS population, most of the patients had an aortic diameter not exceeding the limits for defining a significant aortic dilatation in pediatric MFS population (Table 1), at the time of enrollment in the study. Mean aortic Z-score was  $3.38 \pm 1.23$  at the time when the diagnosis of MFS was formulated, as reported in patients' history. In simple linear regression, all of the analyzed hemodynamic variables (cPP, PPA, peripheral pulse pressure, and PWV) were significantly related with the actual aortic diameter at the Valsalva sinuses (Figure 2), although the strongest correlation was for cPP, and PWV showed only a weak correlation (Table 3). After adjusting for confounders, cPP and PPA remained significant predictors of aortic diameters at Valsalva sinuses, whereas the relations

with peripheral PP and PWV disappeared. In adjusted correlations, PPA was also a significant predictor of aortic diameter at the annulus level. In the adjusted model, no association was found between hemodynamic variables and aortic diameters at the sinotubular junction or at the ascending aorta. No multicollinearity was found between variables in the analyzed regression models. Data were analyzed separately in patients not taking a  $\beta$ -blocker therapy ( $n=44$ ), in comparison with controls and in the correlations with aortic root diameter (Table 4).

The diagnostic power of the examined hemodynamic variables for identifying an aortic diameter exceeding normal limits was evaluated for patients with Z-score  $\geq 2$  ( $n=23$ ). The highest AUC was for PPA ( $0.616 \pm 0.079$ ), whereas AUC for cPP was  $0.502 \pm 0.083$ . For Z-score  $\geq 3$  ( $n=10$ ), the AUC for PPA was  $0.566 \pm 0.090$ , and for cPP  $0.489 \pm 0.109$ . A cutoff of 20% for PPA led to good sensitivity for aortic Z-score  $\geq 2$  or  $\geq 3$  (70%), despite an average degree of specificity (54% for Z-score  $\geq 2$  and 50% for  $\geq 3$ ).

### Aortic Diameters at 1-Year Follow-up

Thirty-six patients were examined after 1-year follow-up (mean follow-up time,  $1.14 \pm 0.32$  years). Mean aortic diameter at the Valsalva sinuses at follow-up was  $33.5 \pm 4.5$  mm (Z-score,

**Table 2.** Sex Differences in Anthropometric and Hemodynamic Variables

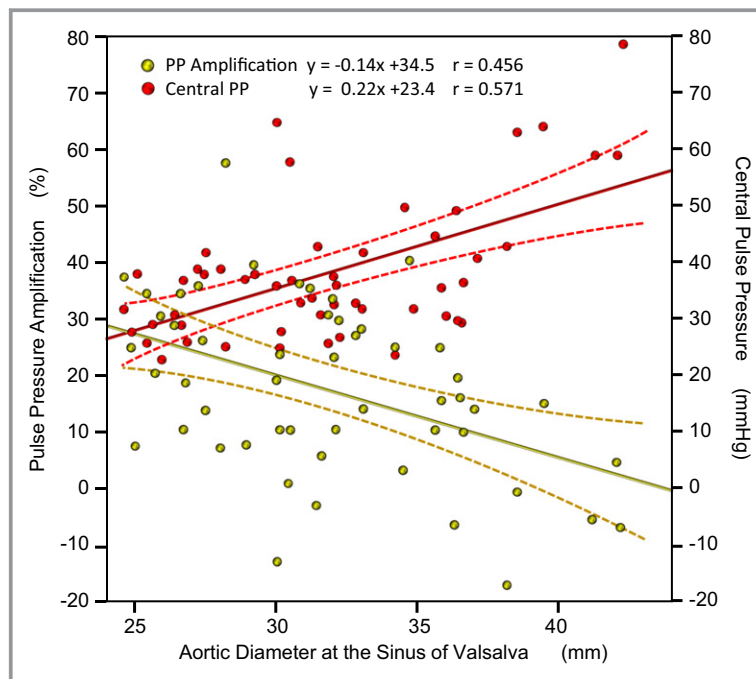
Parameters	Males (n=29)	Females (n=22)	P Value
General characteristics			
Age, y	11.5±3.2	12.6±3.3	0.23
BMI Z-score	-0.49±1.66	-1.00±1.39	0.25
Height Z-score	2.13± 1.58	2.04± 1.09	0.81
Mean arterial pressure, mm Hg	71.2±8.1	70.0±7.7	0.60
Peripheral pulse pressure, mm Hg	46.0±12.3	41.0±5.7	0.06
Heart rate, bpm	73.2±18.4	73.2±11.5	0.99
Aortic diameter (Valsalva sinuses), mm	31.8±5.2	31.6±3.98	0.89
Aortic Z-score	1.68±1.16	1.96±1.17	0.39
Hemodynamic parameters			
Central pulse pressure, mm Hg	41.2±14.9	34.3±5.6	0.003
Pulse pressure amplification, mm Hg	15.8±16.6	20.6±13.2	0.25
Carotid-femoral PWV, m/s	4.79±0.87	5.23±1.13	0.14

Data are reported as mean±SD. BMI indicates body mass index; PWV, pulse wave velocity.

2.12±1.07). Mean increase of aortic diameter at the Valsalva sinuses and of Z-score was, respectively, 1.02±1.25 mm and 0.10±0.39. Twenty-four patients increased their aortic Z-score at the follow-up (Z-INC; mean difference in Z-score, 0.26±0.25), whereas 12 decreased their Z-scores (Z-DEC; mean difference in Z-score, -0.22±0.26). cPP at baseline was significantly higher in the Z-INC compared with the Z-DEC group (42.7±14.2 versus 32.3±5.9 mm Hg;  $P=0.004$ ; Figure 3A), whereas PPA (Z-INC, 13.2±16.1%; Z-DEC, 32.3±5.9%;  $P=0.14$ ; Figure 3B) and PWV (Z-INC, 5.05±1.05 m/s; Z-DEC, 4.98±1.01 m/s;  $P=0.88$ ; Figure 3C) were not significantly different between the 2 groups.

### Correlation of Hemodynamic Variables With FBN1 Genotype

Genetic data were available for 45 patients (88.4%). The remaining patients refused to give consent to genetic analysis or to data publication (5 patients), or genetic data analysis was not completed (1 patient). A pathogenic FBN1 mutation was identified in 40 patients (78.4%). Patients with a positive FBN1 mutation had a cPP of 38.7±13.3 mm Hg and a PPA of 18.2±16.1%, showing no significant difference with patients with negative FBN1 mutation (cPP, 37.5±5.5 mm Hg,  $P=0.828$ ; PPA, 17.8±13.5%,  $P=0.952$ ). Among patients with FBN1 mutation, 26 had a “dominant-negative” FBN1 mutation, whereas 14 had a “haploinsufficient” mutation. There was no



**Figure 2.** Correlation between central pulse pressure and pulse pressure amplification with aortic diameter at the Valsalva sinuses. Red dots: central pulse pressure. Yellow dots: pulse pressure amplification. PP indicates pulse pressure.

**Table 3.** Relationships Between Hemodynamic Variables and Aortic Diameters

Aorta	Central PP		PP Amplification		Peripheral PP		PWV	
	r/ $\beta$	P Value	r/ $\beta$	P Value	r/ $\beta$	P Value	r/ $\beta$	P Value
<b>Annulus</b>								
Univariate (r)	0.543	<0.001	-0.495	<0.001	0.397	0.008	0.245	0.083
Adjusted ( $\beta$ )	0.248	0.068	-0.294	0.008	0.136	0.275	0.040	0.746
<b>Sinuses of Valsalva</b>								
Univariate (r)	0.578	<0.001	-0.468	0.001	0.419	0.005	0.279	0.048
Adjusted ( $\beta$ )	0.371	0.010	-0.271	0.026	0.245	0.088	0.131	0.317
<b>ST junction</b>								
Univariate (r)	0.404	0.003	-0.266	0.059	0.212	0.166	0.352	0.011
Adjusted ( $\beta$ )	0.197	0.200	-0.093	0.470	0.054	0.726	0.215	0.111
<b>Ascending aorta</b>								
Univariate (r)	0.385	0.005	-0.209	0.141	0.205	0.182	0.381	0.006
Adjusted ( $\beta$ )	0.100	0.493	-0.022	0.854	-0.020	0.893	0.205	0.103

Models adjusted for age, sex, body mass index Z-score, mean arterial pressure, and heart rate (for central PP and PP amplification) or left ventricular ejection time (for PWV). PP indicates pulse pressure; PWV, carotid-femoral pulse wave velocity; ST, sino-tubular.

significant difference either in cPP or in PPA between these 2 groups (dominant negative: cPP,  $38.7 \pm 14.7$  mm Hg,  $P=0.979$ ; PPA,  $20.2 \pm 15.6\%$ ; haploinsufficient: cPP,  $38.8 \pm 10.8$  mm Hg,  $P=0.979$ ; PPA,  $14.6 \pm 16.9\%$ ,  $P=0.292$ ).

## Discussion

Our study is the first providing evidence of the early hemodynamic abnormalities occurring in patients with MFS in pediatric age. The importance of the evaluation of central BP values in children and adolescents with MFS emerges from our data: cPP and PPA are significantly and independently correlated with the aortic diameter at the Valsalva sinuses, measured with Doppler echocardiography, the only currently validated risk marker for aortic dissection. An increase in cPP and a reduction in PPA are present when comparing MFS with healthy BP-matched controls, although aortic stiffness, measured as PWV, seems to be the same as the general population.

Our data clearly demonstrate that when only peripheral BP values are considered in pediatric MFS patients, some clinically relevant information is lost. Variables derived from central BP profile (cPP and PPA) are able to identify the subtle hemodynamic abnormalities of the vascular system present in the earliest age. Central BP can be easily assessed with noninvasive methodologies, such as arterial tonometry, which can be performed in an ambulatory setting. Previous studies that evaluated central hemodynamics in MFS have considered only small populations<sup>10</sup> or focused on parameters different than central BP.<sup>32,33</sup> Nevertheless, our study is the first

examining central hemodynamics carried out only in a pediatric MFS population.

A possible explanation of the reduced BP amplification in MFS, causing the observed differences in PPA and cPP, resides in the wave reflections phenomenon. Our data suggest that MFS is characterized by enhanced wave reflections in younger ages, which cause an elevation in central, rather than peripheral, BP values, consistently with previous studies performed with magnetic resonance imaging methodology.<sup>33</sup> The resulting enhancement of cPP induces a repetitive pulsatile stress to the aortic root, which is potentially detrimental. Alterations in central hemodynamics could be the only clinically measurable parameters in the early phases of the disease, where aortic root dilatation is still absent.

In our study, the finding of an increased cPP and a reduced PPA in patients with a Z-score less than 2 further supports this hypothesis. The significant independent correlations found in our study between central BP parameters and aortic root diameters, currently the only validated marker for aortic dissection risk, suggests that the more these parameters are altered, the worse is the aortic phenotype. Although the evaluation of central BP parameters by arterial tonometry, in a clinical setting, could not replace Doppler echocardiography for the identification of a significant dilatation and for the stratification of dissection risk, the finding of altered central hemodynamic variables may be considered a “red flag” to identify patients carrying a higher probability to have, or to develop, an aortic dilatation, and deserving an accurate imaging and a short follow-up. The finding of a significantly higher baseline cPP in patients developing an increase of the

**Table 4.** General Characteristics, Hemodynamic Parameters, and Correlations With Aortic Diameters at the Valsalva Sinuses of Marfan Syndrome Patients Not Taking  $\beta$ -Blockers

Parameters	Marfan Without $\beta$ -Blockers (n=44)	P vs Controls (n=80)
General characteristics		
Sex (males/females)	23/21	0.18
Age, y	11.9 $\pm$ 3.4	0.99
BMI Z-score	-0.80 $\pm$ 1.59	0.80
Height Z-score	2.01 $\pm$ 1.36	<0.0001
Mean arterial pressure, mm Hg	71.3 $\pm$ 7.6	0.86
Peripheral pulse pressure, mm Hg	43.1 $\pm$ 9.4	0.73
Heart rate, bpm	74.5 $\pm$ 15.2	0.92
Hemodynamic parameters		
Central pulse pressure, mm Hg	36.6 $\pm$ 10.8	0.076
Pulse pressure amplification, mm Hg	20.3 $\pm$ 14.1	<0.0001
Carotid-femoral PWV, m/s	5.03 $\pm$ 0.93	0.052
Correlations with aortic root diameter		
Central pulse pressure, r (p)	0.466 (0.001)	
Pulse pressure amplification, r (p)	-0.329 (0.029)	
Carotid-femoral PWV, r (p)	0.330 (0.029)	

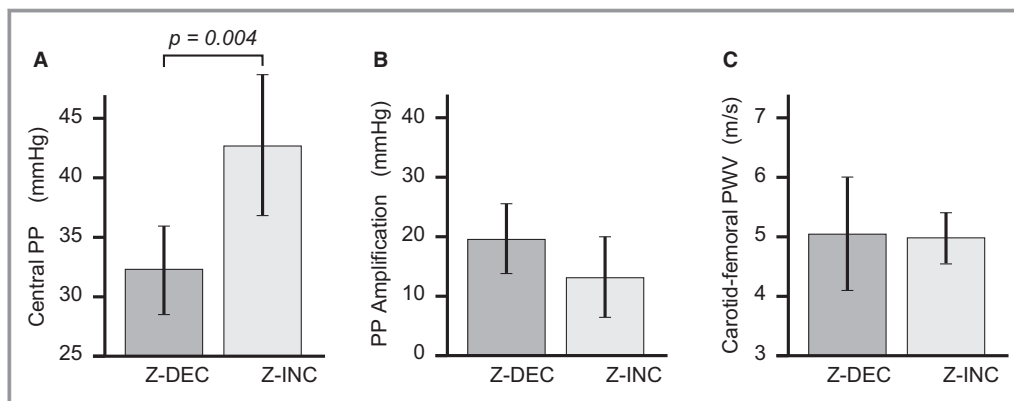
Data are reported as mean $\pm$ SD. BMI indicates body mass index; p, significance of the correlation; PWV, pulse wave velocity; r, correlation coefficient.

aortic Z-score after a 1-year follow-up further reinforce the hypothesis of a causal relationship between altered central pulsatile load and the development of aortic dilatation. Even if the measurement of aortic diameters should remain the mainstay for the management of aortic dilatation in MFS, the evaluation of central hemodynamics could provide some additional information. By the analysis of AUC, a PPA less than 20% appears to be the central hemodynamic alteration with

the highest predictive value for an aortic dilatation. An increase in cPP may be instead an important element to predict a worsening in aortic dilatation, as suggested by our prospective data. Nevertheless, given that BP, both central or peripheral, is an age-dependent parameter in the pediatric age, additional studies, with a larger sample size and a longer follow-up, are required to find the correct cut-off values for a careful management of patients based on cPP or PPA. Central BP percentiles for the pediatric age, which could be a useful tool for the clinical management of this parameter in pediatric MFS, are unfortunately not yet available.

Robust evidence exists regarding the role of transforming growth factor- $\beta$  signaling in the modulation of the general and aortic manifestations of MFS.<sup>34</sup> Transforming growth factor- $\beta$  could be involved also in the process of aortic stiffening in MFS, given that it is implied in the pathological changes occurring in arterial aging and in vascular fibrosis, by reducing collagenase production and stimulating the expression of tissue inhibitors of metalloproteinases, leading to the increase of collagen and fibronectin in the extracellular matrix. Vascular fibrosis and extracellular matrix remodeling are indeed the main mechanisms involved in the process of arterial stiffening,<sup>35</sup> which can be quantified by the variables measured in our study (cPP, PPA, and PWV). Our results suggest that in children and adolescents with MFS, some of these variables (cPP and PPA) are impaired, and could be considered as an intermediate end point, between the increase of transforming growth factor- $\beta$  signaling and onset of aortic dilation.

Considering previous studies that investigated aortic stiffness in MFS, the absence of a significant difference in PWV between Marfan and controls at younger ages is not surprising. The process of aortic stiffening, which becomes measurable with an increase in PWV, is in fact age dependent, as demonstrated by previous studies, using either arterial tonometry<sup>33</sup> or magnetic resonance imaging.<sup>36</sup> A different



**Figure 3.** Central pulse pressure (A), pulse pressure amplification (B), and carotid-femoral pulse wave velocity (C) in patients that increased (Z-INC) or decreased (Z-DEC) the aortic Z-score at the 1-year follow-up. PP indicates pulse pressure; PWV, pulse wave velocity.



rate of increase in PWV with age is present in MFS compared with the general population,<sup>12</sup> because the process of arterial wall stiffening continues all along one's lifetime and produces an earlier arterial aging in MFS.

Recent studies on the pathophysiology of MFS<sup>4</sup> have reported sex differences in the development of aortic complications, with aortic aneurysms and aortic surgery more frequently occurring in men than in women. Although our study was not designed to detect sex differences in arterial wall properties parameters, we found a significant increase in cPP in males compared with females. This hemodynamic difference, if confirmed in further studies, could be an additional element for understanding the sex differences in aortic involvement in MFS patients.

In our study, there was no significant difference in the central BP parameters between patients with a haploinsufficient or a dominant-negative FBN1 mutation. The haploinsufficient genotype (causing a reduced amount of FBN1 protein) has been demonstrated to be an independent risk factor for cardiovascular death and aortic dissection compared with a dominant-negative genotype in adults.<sup>5</sup> From our data, it seems that, at least in early ages, there is no difference in the pulsatile hemodynamics between these 2 genotypes. Nevertheless, a different progression cannot be excluded, with differences in the hemodynamic profile according to the mutation type that could become evident and clinically relevant at a later age. It should be acknowledged that our study was not specifically designed for finding a difference between these 2 genotype groups, and that a larger sample size and a longer follow-up are probably needed for this purpose. Another possibility is that medications might have masked the difference in vascular properties between the 2 types of FBN1 mutations, given that previous evidence suggested that Losartan beneficial outcome is more pronounced in patients carrying a haploinsufficient than a dominant-negative mutation.<sup>30</sup>

Other limitations of our study should be mentioned. First, a large majority of MFS patients were treated with antihypertensive medications for slowing the rate of progression of aortic dilatation. Given that renin-angiotensin-aldosterone system blockers and  $\beta$ -blockers have been shown to affect PWV and parameters derived from pulse wave analysis,<sup>37</sup> we hypothesize that a greater difference between Marfan and control patients could have been found, even for PWV, in the absence of treatment, given that such a difference is likely to have been masked because of concomitant drug therapy in MFS. Medications could also cause significant differences in central BP parameters given that  $\beta$ -blockers are known to influence less central than peripheral BP values, compared with other antihypertensive classes, and to reduce amplification of BP.<sup>38</sup> Considering these drug-related effects, our conclusions about the diagnostic and prognostic value of

central BP parameters should be tempered in patients in therapy with a beta-blocker. Nevertheless, in our study, only a few patients were using  $\beta$ -blockers and most of them did not even receive a full dosage. The observed differences in PPA and the correlations with aortic diameters remained significant after excluding these patients (Table 3). Regarding therapy with renin-angiotensin-aldosterone system blockers, this class of drug is known to reduce arterial stiffness, and eventually to reduce related parameters, such as cPP or PWV. Therefore, the observed differences between MFS patients and controls could have even been more pronounced, in the absence of renin-angiotensin-aldosterone system blocker therapy.

A possible confounder, in our study, is the different body size that is typical of MFS. Children with MFS were significantly taller than matched controls, given that it was not possible to select a control population matched for the stature. Stature has been described as a determinant of PPA indeed. But higher stature, with a higher aortic length, has a direct positive relationship with pressure amplification.<sup>25,39</sup> Therefore, our MFS patients showed a reduced PPA despite their higher stature, and the observed differences could even be higher. However, the correlation of cPP and PPA with height was not strong in our study sample, both for Marfan and controls. The lack of this correlation could be explained by the phenomenon of dampening of the pulse waves, typical of the young subjects,<sup>11</sup> and because taller MFS patients showed a reduced PPA, probably because characterized by a worse global (vascular and dysmorphological) phenotype.

This study shows that central BP parameters are significantly altered in children and adolescent patients affected by MFS, independently of FBN1 genotype. Aortic PWV is not significantly different from the general population in this age group. cPP and PPA are independently associated with diameter of aorta at the sinuses of Valsalva, which is a validated marker of aortic dissection risk. Central BP parameters, such as cPP or PPA, derived from a noninvasive methodology (arterial applanation tonometry), which have been used for the first time in a large group of pediatric Marfan patients, have shown a good ability to identify the earliest hemodynamic abnormalities in MFS. By analyzing the aortic diameters of patients after 1 year, we observed that an increased cPP is present among patients whose aortic dilatation worsened in the follow-up. Further longitudinal studies are needed to validate the predictive ability of central BP for the assessment of aortic dissection risk or as a target for specific therapies in MFS.

## Disclosures

Paolo Salvi reports consultant activities from DiaTecne s.r.l. The remaining authors have no disclosures to report.

## References

- Groenink M, Rozendaal L, Naef MS, Hennekam RC, Hart AA, van der Wall EE, Mulder BJ. Marfan syndrome in children and adolescents: predictive and prognostic value of aortic root growth for screening for aortic complications. *Heart*. 1998;80:163–169.
- Faivre L, Masurel-Paulet A, Collod-Beroud G, Callewaert BL, Child AH, Stheneur C, Binquet C, Gautier E, Chevallier B, Huet F, Loeyls BL, Arbustini E, Mayer K, Arslan-Kirchner M, Kiotsekoglou A, Comeglio P, Grasso M, Halliday DJ, Beroud C, Bonithon-Kopp C, Claustres M, Robinson PN, Ades L, De Backer J, Coucke P, Francke U, De Paepe A, Boileau C, Jondeau G. Clinical and molecular study of 320 children with Marfan syndrome and related type I fibrillinopathies in a series of 1009 probands with pathogenic FBN1 mutations. *Pediatrics*. 2009;123:391–398.
- Mueller GC, Stark V, Steiner K, von Kodolitsch Y, Rybczynski M, Weil J, Mir TS. Impact of age and gender on cardiac pathology in children and adolescents with Marfan syndrome. *Pediatr Cardiol*. 2013;34:991–998.
- Roman MJ, Devereux RB, Preiss LR, Asch FM, Eagle KA, Holmes KW, LeMaire SA, Maslen CL, Milewicz DM, Morris SA, Prakash SK, Pyeritz RE, Ravekes WJ, Shohet RV, Song HK, Weinsaft JW; Gen TACI. Associations of age and sex with Marfan phenotype: the National Heart, Lung, and Blood Institute GenTAC (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions) Registry. *Circ Cardiovasc Genet*. 2017;10:pii: e001647
- Franken R, Groenink M, de Waard V, Feenstra HM, Scholte AJ, van den Berg MP, Pals G, Zwinderman AH, Timmermans J, Mulder BJ. Genotype impacts survival in Marfan syndrome. *Eur Heart J*. 2016;37:3285–3290.
- Lacro RV, Dietz HC, Sleeper LA, Yetman AT, Bradley TJ, Colan SD, Pearson GD, Selamet Tierney ES, Levine JC, Atz AM, Benson DW, Braverman AC, Chen S, De Backer J, Gelb BD, Grossfeld PD, Klein GL, Lai WW, Liou A, Loeyls BL, Markham LW, Olson AK, Paridon SM, Pemberton VL, Pierpont ME, Pyeritz RE, Radojewski E, Roman MJ, Sharkey AM, Stylianou MP, Wechsler SB, Young LT, Mahony L; Pediatric Heart Network Investigators. Atenolol versus losartan in children and young adults with Marfan's syndrome. *N Engl J Med*. 2014;371:2061–2071.
- Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, Invitti C, Litwin M, Mancia G, Pall D, Rascher W, Redon J, Schaefer F, Seeman T, Sinha M, Stabouli S, Webb NJ, Wuhl E, Zanchetti A. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. *J Hypertens*. 2016;34:1887–1920.
- Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, Umans JG, Howard BV. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension*. 2007;50:197–203.
- Milan A, Tosello F, Caserta M, Naso D, Puglisi E, Magnino C, Comoglio C, Rabbia F, Mulaturo P, Veglio F. Aortic size index enlargement is associated with central hemodynamics in essential hypertension. *Hypertens Res*. 2011;34:126–132.
- Jondeau G, Boutouyrie P, Lacombe P, Laloux B, Dubourg O, Bourdarias JP, Laurent S. Central pulse pressure is a major determinant of ascending aorta dilation in Marfan syndrome. *Circulation*. 1999;99:2677–2681.
- Salvi P. *Pulse Waves. How Vascular Hemodynamics Affects Blood Pressure*. 2nd ed. Heidelberg, Germany: Springer Nature; 2017.
- Salvi P, Grillo A, Marelli S, Gao L, Salvi L, Viecca M, Di Blasio AM, Carretta R, Pini A, Parati G. Aortic dilatation in Marfan syndrome: role of arterial stiffness and fibrillin-1 genotype. *J Hypertens*. 2017; In-press. DOI: 10.1097/HJH.0000000000001512.
- Bradley TJ, Potts JE, Potts MT, DeSouza AM, Sandor GG. Echocardiographic Doppler assessment of the biophysical properties of the aorta in pediatric patients with the Marfan syndrome. *Am J Cardiol*. 2005;96:1317–1321.
- Akazawa Y, Motoki N, Tada A, Yamazaki S, Hachiya A, Matsuzaki S, Kamiya M, Nakamura T, Kosho T, Inaba Y. Decreased aortic elasticity in children with Marfan syndrome or Loeyls-Dietz syndrome. *Circ J*. 2016;80:2369–2375.
- Prakash A, Adlakha H, Rabideau N, Hass CJ, Morris SA, Geva T, Gauvreau K, Singh MN, Lacro RV. Segmental aortic stiffness in children and young adults with connective tissue disorders: relationships with age, aortic size, rate of dilation, and surgical root replacement. *Circulation*. 2015;132:595–602.
- Salvi P, Grillo A, Parati G. Noninvasive estimation of central blood pressure and analysis of pulse waves by applanation tonometry. *Hypertens Res*. 2015;38:646–648.
- Loeyls BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, Hilhorst-Hofstee Y, Jondeau G, Faivre L, Milewicz DM, Pyeritz RE, Sponseller PD, Wordsworth P, De Paepe AM. The revised Ghent nosology for the Marfan syndrome. *J Med Genet*. 2010;47:476–485.
- Reusz GS, Cseperekal O, Temmar M, Kis E, Cherif AB, Thaleb A, Fekete A, Szabo AJ, Benetos A, Salvi P. Reference values of pulse wave velocity in healthy children and teenagers. *Hypertension*. 2010;56:217–224.
- Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E; Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC); Association for European Paediatric Cardiology (AEPC); ESC Committee for Practice Guidelines (CPG). ESC guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J*. 2010;31:2915–2957.
- Colan SD, McElhinney DB, Crawford EC, Keane JF, Lock JE. Validation and re-evaluation of a discriminant model predicting anatomic suitability for biventricular repair in neonates with aortic stenosis. *J Am Coll Cardiol*. 2006;47:1858–1865.
- van Kimmenade RR, Kempers M, de Boer MJ, Loeyls BL, Timmermans J. A clinical appraisal of different z-score equations for aortic root assessment in the diagnostic evaluation of Marfan syndrome. *Genet Med*. 2013;15:528–532.
- Salvi P, Lio G, Labat C, Ricci E, Pannier B, Benetos A. Validation of a new non-invasive portable tonometer for determining arterial pressure wave and pulse wave velocity: the pulsepen device. *J Hypertens*. 2004;22:2285–2293.
- Joly L, Perret-Guillaume C, Kearney-Schwartz A, Salvi P, Mandry D, Marie PY, Karcher G, Rossignol P, Zannad F, Benetos A. Pulse wave velocity assessment by external noninvasive devices and phase-contrast magnetic resonance imaging in the obese. *Hypertension*. 2009;54:421–426.
- Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588–2605.
- Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, Roman MJ, Safar ME, Segers P, Smulyan H. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension*. 2009;54:375–383.
- Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. *J Physiol*. 2000;525(Pt 1):263–270.
- Reference Values for Arterial Stiffness Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J*. 2010;31:2338–2350.
- Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, Filipovsky J, Huybrechts S, Mattace-Raso FU, Protogerou AD, Schillaci G, Segers P, Vermeersch S, Weber T. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens*. 2012;30:445–448.
- Collod-Beroud G, Le Bourdelles S, Ades L, Ala-Kokko L, Booms P, Boxer M, Child A, Comeglio P, De Paepe A, Hyland JC, Holman K, Kaitila I, Loeyls B, Matyas G, Nuytink L, Peltonen L, Rantamaki T, Robinson P, Steinmann B, Junien C, Beroud C, Boileau C. Update of the UMD-FBN1 mutation database and creation of an FBN1 polymorphism database. *Hum Mutat*. 2003;22:199–208.
- Franken R, den Hartog AW, Radonic T, Micha D, Mauerer A, van Dijk FS, Meijers-Heijboer HE, Timmermans J, Scholte AJ, van den Berg MP, Groenink M, Mulder BJ, Zwinderman AH, de Waard V, Pals G. Beneficial outcome of losartan therapy depends on type of FBN1 mutation in Marfan syndrome. *Circ Cardiovasc Genet*. 2015;8:383–388.
- Salvi P, Palombo C, Salvi GM, Labat C, Parati G, Benetos A. Left ventricular ejection time, not heart rate, is an independent correlate of aortic pulse wave velocity. *J Appl Physiol (1985)*. 2013;115:1610–1617.
- Mortensen K, Aydin MA, Rybczynski M, Baulmann J, Schahidi NA, Kean G, Kuhne K, Bernhardt AM, Franzen O, Mir T, Habermann C, Koschyk D, Ventura R, Willems S, Robinson PN, Berger J, Reichenspurner H, Meinertz T, von Kodolitsch Y. Augmentation index relates to progression of aortic disease in adults with Marfan syndrome. *Am J Hypertens*. 2009;22:971–979.
- Segers P, De Backer J, Devos D, Rabben SI, Gillebert TC, Van Bortel LM, De Sutter J, De Paepe A, Verdonck PR. Aortic reflection coefficients and their association with global indexes of wave reflection in healthy controls and patients with Marfan's syndrome. *Am J Physiol Heart Circ Physiol*. 2006;290:H2385–H2392.
- Lindsay ME, Dietz HC. Lessons on the pathogenesis of aneurysm from heritable conditions. *Nature*. 2011;473:308.
- Harvey A, Montezano AC, Lopes RA, Rios F, Touyz RM. Vascular fibrosis in aging and hypertension: molecular mechanisms and clinical implications. *Can J Cardiol*. 2016;32:659–668.
- Westenberg JJ, Scholte AJ, Vaskova Z, van der Geest RJ, Groenink M, Labadie G, van den Boogaard PJ, Radonic T, Hilhorst-Hofstee Y, Mulder BJ, Kroft LJ, Reiber JH, de Roos A. Age-related and regional changes of aortic stiffness in the Marfan syndrome: assessment with velocity-encoded MRI. *J Magn Reson Imaging*. 2011;34:526–531.

37. Ong KT, Delorme S, Pannier B, Safar ME, Benetos A, Laurent S, Boutouyrie P; investigators. Aortic stiffness is reduced beyond blood pressure lowering by short-term and long-term antihypertensive treatment: a meta-analysis of individual data in 294 patients. *J Hypertens*. 2011;29:1034–1042.
38. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the conduit artery function evaluation (cafe) study. *Circulation*. 2006;113:1213–1225.
39. London GM, Guerin AP, Pannier B, Marchais SJ, Stimpel M. Influence of sex on arterial hemodynamics and blood pressure. Role of body height. *Hypertension*. 1995;26:514–519.