Chapter

Arterial Stiffness Assessment in Children with Familial Hypercholesterolemia

Dinara Sadykova, Liliia Galimova, Evgeniia Slastnikova, Zulfiia Khabibrakhmanova and Natalya Guseva

Abstract

Familial hypercholesterolemia (FH) is the genetic disease which characterized by an increase of level total cholesterol and low density lipoproteins since childhood. The aim of the study was to assess arterial stiffness in children with heterozygous FH by measuring the pulse wave velocity (PWV) in the aorta. The study involved 118 children, 60 healthy children in the control group and 58 children with heterozygous FH in the main group. Both groups were divided into 3 age subgroups: 5–7 years old, 8–12 years old and 13–17 years old. The diagnosis of FH was made using British criteria by Simon Broome. The lipid profile was determined for all children, blood pressure was monitored daily with an estimate of the minimum, mean and maximum PWV (PWVmin, mean PWV, PWVmax) in aorta using oscillometric method. Correlation analysis in patients with FH revealed direct correlation between PWVmin, mean PWV and PWVmax with total cholesterol ($r = 0.46$, $r = 0.46$ and $r = 0.464$, respectively, $p < 0.001$). The study demonstrates an increase in the PWV in the aorta in children with FH compared with healthy peers from 8–12 years of age and a progression of arterial stiffness most significant in the group of 13–17 years.

Keywords: familial hypercholesterolemia, arterial stiffness, pulse wave velocity, children

1. Introduction

Familial hypercholesterolemia (FH) is a monogenic disease with a predominantly autosomal dominant mode of inheritance, accompanied by a significant increase of the low-density lipoprotein cholesterol (LDL-C) level in the blood [1]. Patients with FH have a high risk of early development of atherosclerosis [2, 3]. The incidence of FH in the general population is estimated at about 1 per 200 persons [3], in addition, the evidence exist that in patients with established coronary heart disease, the prevalence of potential FH is up to 8.3% in men and 11.1% in women [4]. However, despite this, there is a low level of diagnosis and treatment [5, 6]. In this regard, registers of patients with FH have recently been developed for assessing the level of diagnosis, treatment and improvement in results of therapy [7, 8]. In

more than 90% of cases, FH is caused by mutations in the gene encoding the LDL receptor, which reduce the cellular uptake of LDL and, therefore, significantly increase their plasma level [9]. Mutations in other genes leading to the same phenotype have also been identified: associated with apolipoprotein B, which affect the LDL-binding domain of apolipoprotein B as the most important apolipoprotein for uptake of LDL particles, and mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9) [10, 11].

It is known that high plasma cholesterol level is a risk factor for the development of cardiovascular diseases [12] and may be the cause of early vascular damage. Currently, there are methods that allow registering pathological changes in blood vessels at preclinical stage. The detection of early changes in the walls of arteries by non-invasive methods, such as ultrasound duplex scanning, assessment of central aortic pressure and pulse wave velocity, has opened up new perspectives, helping to identify high-risk patients [13–17].

Several studies have shown that hypercholesterolemia can cause the loss of elasticity and increased stiffness of arterial vessels, leading to an increase in the pulse wave velocity due to its rapid spreading in stiff arteries [18, 19]. Arterial stiffness is considered to be a significant predictor of overall and cardiovascular mortality in patients with arterial hypertension [20–23], in patients with end-stage renal failure [24, 25] and in the elderly patients [26]. In addition, it was noted that arterial stiffness is closely related to structural changes in the artery such as thickening of the intima-media complex [27]. Changes in the elastic properties of arteries may indicate a functional disorder long before the appearance of clinical symptoms. One of the indicators for assessing the stiffness of the arteries is the pulse wave velocity (PWV) measurement in aorta. It is the measurement of the speed of pulse pressure propagation along a segment of the arterial vessels [28]. It should be noted that the measurement of the arterial stiffness is quite widespread among adult patients [29, 30], while in pediatrics, despite its non-invasiveness and high informativeness, it is used much less frequently. This is probably due to the complexity of standardization, time costs and the need for additional equipment.

2. The aim of this study

The aim of this study is to assess arterial stiffness in children with heterozygous familial hypercholesterolemia by measuring the pulse wave velocity in the aorta

3. Materials and methods

The study involved 118 children. The control group consisted of 60 healthy children and 58 children with heterozygous familial hypercholesterolemia formed the main group (**Table 1**). The diagnosis of FHC was established in accordance with the British Simon Broome criteria [31]. The study included children with FH who were not taking statins. 15 patients from the main group underwent genetic testing in the Health in Code laboratory (Spain) for the detection of a monogenic mutation responsible for the development of familial hypercholesterolemia, and a positive DNA test was obtained. Exclusion criteria: secondary dyslipidemia, arterial hypertension, obesity. Written informed consent was obtained from all the participants of the study.

	Control group, n = 60	**Main group, n = 58**
Age, years (M ± σ)	11,53 ± 4,2	10,92 ± 4,1
Gender, m/f	40/20	37/21
Smoking, n/%	0(0)	0(0)
Obesity, n/%	0(0)	0(0)
Arterial hypertension, n/%	0(0)	0(0)
Cutaneous xanthomas	0(0)	0(0)
Corneal arch	0(0)	0(0)
Thickening of the Achilles tendon	0(0)	0(0)
TC, mmol/l (M ± σ)	3,5 ± 1,2	7,8 ± 2,3
LDL, mmol/l (M ± σ)	1,6 ± 0,8	6,1 ± 1,2
HDL, mmol/l (M ± σ)	0,9 ± 0,1	1,1 ± 0,3
TG, mmol/l (M ± σ)	0,8 ± 0.4	1,2 ± 0,3

Abbreviations: TC - total cholesterol; LDL - low density lipoprotein; HDL - high density lipoprotein; TG - triglycerides.

Table 1.
Clinical and laboratory characteristics of children of the main and control groups.

Total cholesterol, triglycerides, LDL, and high-density lipoprotein cholesterol (HDL) were measured using commercial kits (Beckman Coulter, USA) on an automatic biochemical analyzer (Au5800 Beckman Coulter, USA).

The clinical examination included a careful life history and family history taking, physical examination, and body mass index (BMI) assessment. All children underwent 24-hour blood pressure monitoring with an assessment of the pulse wave velocity in the aorta using the oscillometric method of the BPLab Vasotens system (Petr Telegin Ltd., Russia).

In the BPLab program for determining PWV in aorta the following ratio is used: PWVaorta = K × (2 × L) /RWTT, where PWVaorta is PWV in the aorta; K is the scale factor for standardizing the obtained value of the PWV; L is the length of the aortic trunk (in BPLab software, the distance from the upper edge of the sternum to the pubic bone is taken as the length of the aorta); RWTT (reflected wave transit time) [32].

4. Statistical analysis

Statistical analysis was carried out using the IBM SPSS Statistics v.23 software (developed by IBM Corporation, USA). The results were subjected to statistical processing using nonparametric methods in connection with the established absence of a normal distribution of quantitative indicators (testing for normal distribution was carried out using the Shapiro–Wilk test). Quantitative data were described using the values of the median (Me) and the lower and upper quartiles [Q1-Q3]. Comparison of quantitative indicators between two groups was carried out using the Mann–Whitney test, between the three groups using the Kruskal-Wallis test with an a posteriori Dunn test. Correlation analysis was carried out using the Spearman's rank correlation coefficient; the assessment of the tightness of correlation was carried out using the Chaddock scale. Differences in indicators and identified relationships were considered statistically significant at $p < 0.05$.

5. Results

Analysis of the values of the minimum PWV (PWVmin), mean PWV (PWVmean) and maximum PWV (PWVmax) obtained during 24-hour blood pressure monitoring revealed statistically significant differences between the main and control groups ($p < 0.001$) (**Figure 1**). The presence of FHC was accompanied by a significant increase in PWV - minimum, mean and maximum values.

Taking into account the results obtained, we analyzed the degree of change in PWV depending on the age of children. For the analysis, both groups were divided into 3 age subgroups: from 5 to 7 years old, from 8 to 12 years old, from 13 to 17 years old (**Table 2**).

In accordance with the results obtained, in the younger age subgroup (5–7 years old), there were no statistically significant differences in PWV between the children of the main and control groups. In children aged 8–12 years, there was no statistically significant difference in the values of PWV min and mean PWV. While PWVmax was characterized by statistically significantly higher values in the main group (5.1 [4.7–5.8] m/s) relative to the control (4.6 [4.45–5.05] m/s) ($p = 0.041$). The most pronounced changes were found in the group of children with FHC at the age of 13–17 years. In this group were revealed statistically significant differences in the minimum, mean and maximum pulse wave velocity.

Taking into account the peculiarities of physical parameters and age periodization, we have analyzed the dynamics of changes in PWV depending on the age of children. In children of the control group, PWVmin in children 8–12 year old was statistically significantly higher than in children 5–7 year old (3.6 [3.2–4.1] m/s and 3.0 [2.8–3.1] m/s, respectively, $p = 0.049$). When comparing PWVmin in groups of 8–12 years old children and 13–17 years old children, no statistically significant difference was found (3.6 [3.2–4.1] m/s and 3.9 [3.5–4.1] m/s, respectively, $p = 0.052$). A similar dynamics of growth was observed for the mean pulse wave velocity in healthy children when compared in age subgroups 8–12 years old and 5–7 years old (4.3 [3.7–5.1] m/s and 3.8 [3.7–3.9] m/s, respectively, $p = 0.026$) and 8–12 years old and 13–17 years old (4.3 [3.7–5.1] m/s and 4.5 [4.2–4, 9] m/s, respectively, $p = 0.114$).

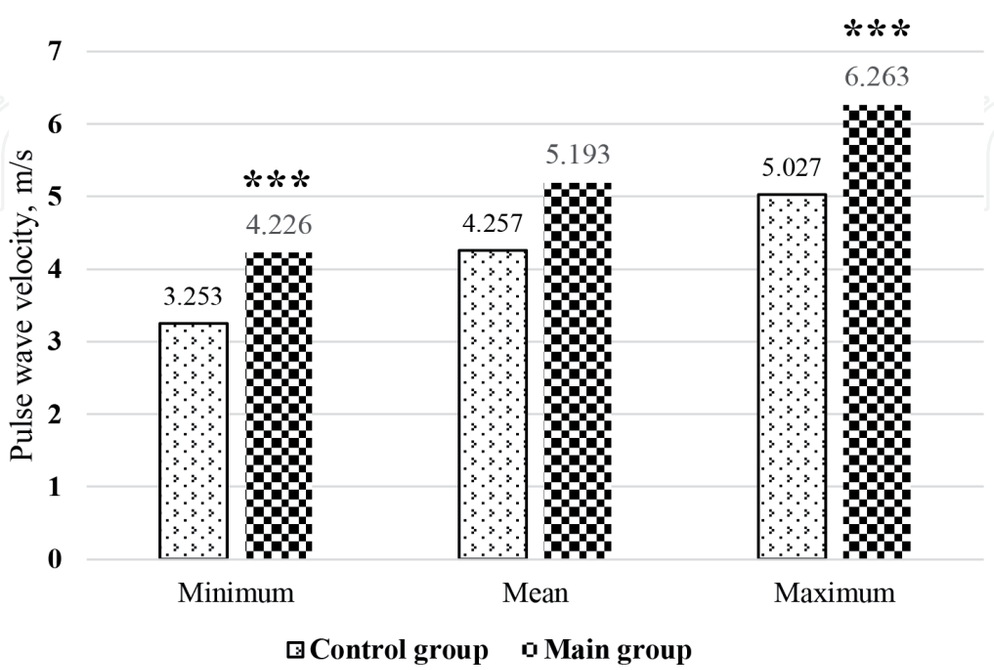

Figure 1.
*Comparison of the values of the pulse wave velocity in the main and control groups. Note: *** - $p < 0.001$.*

Parameter m/s	Control group		Main group		p
	Me	Q_1-Q_3	Me	Q_1-Q_3	
5–7 years (n = 15)			5–7 years (n = 16)		
PWVmin	3,0	2,8-3,1	3,05	2,6-3,3	0,19
PWVmean	3,8	3,7-3,9	4,1	3,8-4,1	0,19
PWVmax	4,5	4,3-4,8	4,8	4,1-5,3	0,095
8–12 years (n = 22)			8–12 years (n = 21)		
PWVmin	3,6	3,2-4,1	3,5	3,3-3,9	0,052
PWVmean	4,3	3,7-5,1	4,6	4,0-5,0	0,05
PWVmax	4,6	4,45-5,05	5,1	4,7-5,8	0,041
13–17 years (n = 21)			13–17 years (n = 23)		
PWVmin	3,9	3,5-4,1	4,7	4,1-5,1	0,009
PWVmean	4,5	4,2-4,9	5,5	4,8-6,4	0,009
PWVmax	5,4	5,05-5,6	6,2	5,7-7,55	0,007

Table 2.
Comparison of the values of the pulse wave velocity depending on the age of the children.

The analysis of PWVmax showed that these indicators in the group of 5–7 years old and 8–12 years old children did not significantly differ from each other (4.5 [4.3–4.8] m/s and 4.6 [4.45–5.05] m/s, p = 0.145), while in children 13–17 years old it was significantly higher in comparison with 8–12 years old children (5.4 [5.05–5.6] m/s and 4.6 [4, 45–5.05] m/s, respectively, p = 0.022). It should be noted that there is a statistically significant difference in the values of PWVmin, mean PWV and PWVmax in children 13–17 years old relatively to 5–7 years old (**Table 3**).

The study of PWV in children of the main group revealed a statistically significant difference in the increase in PWVmin, mean PWV and PWVmax indicators when compared in all main groups (**Table 4**).

Parameter, m/s	5–7 years	8–12 years	13-17 years	P_{1-2}	P_{2-3}	P_{1-3}
PWVmin	3,0 [2,8-3,1]	3,6 [3,2-4,1]	3,9 [3,5-4,1]	**0,049**	0,052	**0,043**
PWVmean	3,8 [3,7-3,9]	4,3 [3,7-5,1]	4,5[4,2-4,9]	**0,026**	0,114	**0,047**
PWVmax	4,5 [4,3-4,8]	4,6 [4,45-5,05]	5,4 [5,05-5,6]	0,145	**0,022**	**0,018**

Note: p is the level of significance of the differences.

Table 3.
Indicators of the pulse wave velocity of children of the control group.

Parameter, m/s	5–7 years	8–12 years	13–17 years	P_{1-2}	P_{2-3}	P_{1-3}
PWVmin	3,05[2,6-3,3]	3,5 [3,3-3,9]	4,7 [4,1-5,1]	**0,001**	**0,004**	**0,008**
PWVmean	4,1 [3,8-4,1]	4,6 [4,0-5,0]	5,5[4,8-6,4]	**0,001**	**0,016**	**0,004**
PWVmax	4,8 [4,1-5,3]	5,1 [4,7-5,8]	6,2 [5,7-7,55]	**0,028**	**0,021**	**0,018**

Note: p is the level of significance of the differences.

Table 4.
Indicators of the pulse wave velocity of children of the main group.

At the same time, a more significant dynamics of increase in PWV was observed in children with FH compared with the control group in the age range of 13–17 years (**Figure 2**). It should be noted that the dynamics of the increase in indicators in the control group was less than in children with FH (**Figure 3**).

Taking into account the presence of dyslipidemia in patients with FH in the form of severe hypercholesterolemia, we performed a correlation analysis of the relationship between PWV values and lipid metabolism indicators. In the main group, statistically significant direct correlations were established between PWVmin, mean PWV and PWVmax with total cholesterol level (r_{xy} = 0.46 [95% CI: 0.227–0.644], r_{xy} = 0.46 [95% CI: 0.229–0.642] and r_{xy} = 0.464 [95% CI: 0.234–0.645], respectively, $p < 0.001$ in all cases).

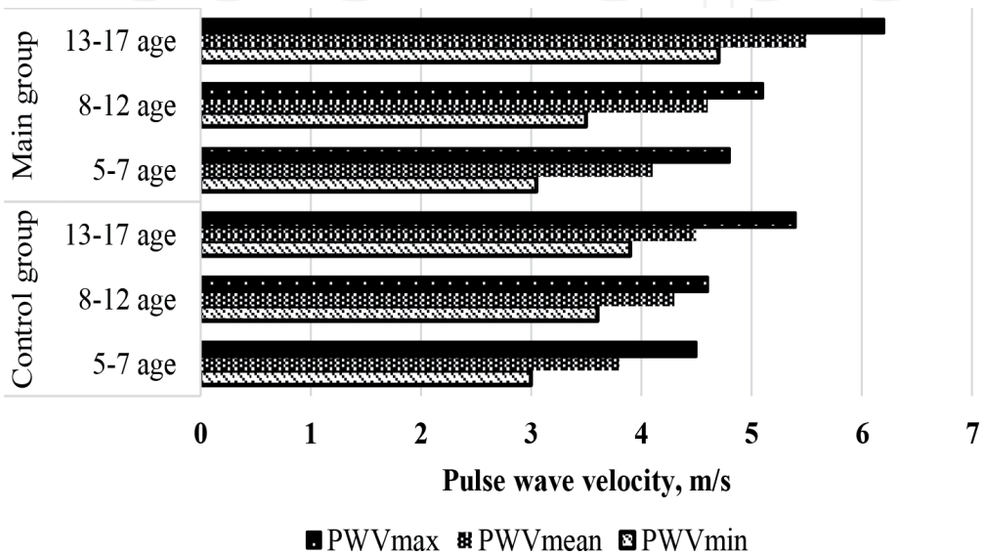

Figure 2.
Indicators of the pulse wave velocity of the main and control groups, depending on the age of the children. Note: PWVmin - minimum pulse wave velocity, PWVmean - mean pulse wave velocity, PWVmax - maximum pulse wave velocity.

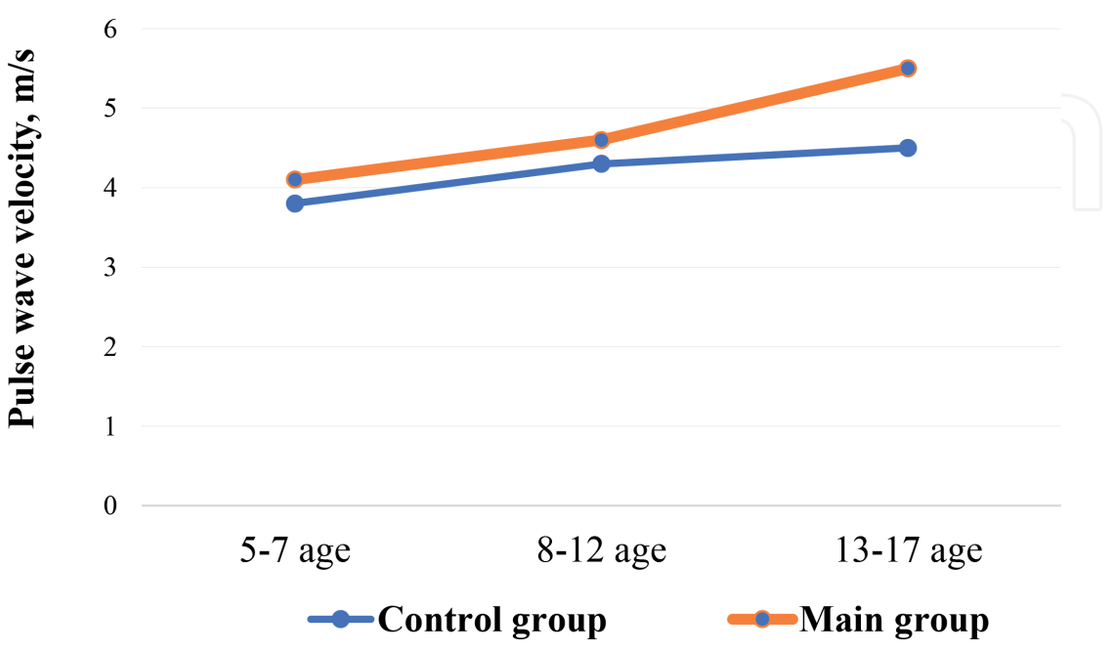

Figure 3.
*Dynamics of the increase in the mean pulse wave velocity in the main and control groups, depending on the age of the children. Note: * - p = 0.009.*

6. Discussion

In the presented study, the condition of the arterial wall was assessed by measuring the pulse wave velocity in the aorta in children with FH and healthy children of the same age. The study design differs from previous studies of PWV in the pediatric population presented in the literature [33–36] in distribution of participants into age subgroups. In our opinion, such an analysis of the PWV values increases the correctness and statistical significance of the obtained results.

We found that the PWV values of children of the main group at the age of 5–7 years do not differ from those of the control group. In the 8–12-year-old subgroup in patients with FH, only the maximum PWV indicators were statistically significantly higher than in the comparison group. The identified deviations probably reflect the initial changes in the stiffness of the vascular wall in children of the main group. The most pronounced differences in the studied parameters were observed in children with FH in the age subgroup of 13–17 years old and were characterized by a statistically significant increase in PWVmin, mean PWV and PWmax relatively to the control group.

In our study, we also analyzed the dynamics of PWV growth depending on age. It was shown that PWV values increase with the age of the child both in familial hypercholesterolemia and in healthy children. This indicates that the studied indicators cannot be the same for all children and it is necessary to use age reference values in pediatrics. In addition, the increase in all three values of PWV was most pronounced in the group of 13–17 year old patients with FH, it allows us to suggest that they have a more pronounced change of properties of the vascular wall already at preclinical stages than in individuals with normal blood lipid profile.

A number of studies have revealed an increased PWV in children with hypertension [37], increased body mass index [38, 39]. In the present study, special attention was paid to patients with FH without risk factors such as smoking, obesity, and high blood pressure. Thus, the authors were able to assess the effect of hypercholesterolemia on the change in PWV precisely. The established correlation between total cholesterol level and PWV values allows us to regard an increase in total cholesterol level as a leading factor in forming the arterial stiffness in children with FH. In addition, the registration of the initial changes in PWV in the group with FH from 8–12 years old with further progression of the process in the absence of such changes in children 5–7 years old indicates a possible cumulative effect of cholesterol and its effect on the artery wall condition. This is consistent with large randomized studies showing that the effect of LDL on the development of atherosclerotic vascular disease is determined not only by the absolute level of LDL, but also by its cumulative effect on target organs [2, 40, 41].

7. Conclusion

Thus, the relationship between cholesterol level, age, and arterial stiffness indicators in familial hypercholesterolemia makes it possible to recommend the study of pulse wave velocity as a possible additional method for studying the cardiovascular risk in children with familial hypercholesterolemia and assessing the progression of the disease

Conflict of interest

Authors declare no conflict of interest.

Acknowledgements

We want to thank the Head of Tatarstan Republic's Ministry of Health, the Rector of Kazan State medical University, Kazan, Russian Federation, the Head of the Children's Republican Clinical Hospital of the Ministry of Health of the Republic of Tatarstan, Russian Federation for the help in the organization of Children's Lipid Center, where we run our observation of children with Familial Hypercholesterolemia.

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