ISSN 1607-419X
ISSN 2411-8524 (Online)
УДК 612.16:616-053.5.12-008.331

Change in the aortic pulse wave velocity in children with familial hypercholesterolemia

L. F. Galimova [1, 2], D. I. Sadykova [2], E. S. Slastnikova [2], D. I. Marapov [2, 3]
[1] Republican Children's Hospital, Kazan, Russia
[2] Kazan State Medical University, Kazan, Russia
[3] Educational and Methodical Center "Economical Technologies in Healthcare"

Corresponding author:
Liliia F. Galimova,
Kazan State Medical University,
49 Butlerova street, Kazan,
420012 Russia.
E-mail: lilu1@inbox.ru

Received 6 April 2020;
accepted 28 August 2020.

Abstract

Background. Familial hypercholesterolemia (FH) is the genetic disease characterized by an increase in the levels of 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 pulse wave velocity (PWV) in the aorta. **Design and methods.** The study involved 118 children. Of these, 60 healthy children were in the control group and 58 children with the diagnosis of heterozygous FH were included in the main group. Both groups were divided into 3 age subgroups: from 5 to 7 years old, from 8 to 12 years old and from 13 to 17 years old. The diagnosis of FH was made according to the British criteria by Simon Broome. The lipid profile was determined for all children, blood pressure was monitored daily with the estimate of the minimum, average and maximum PWV (PWVmin, PWVav, PWVmax) in aorta using oscillometric method. **Results.** In the younger age subgroup (5–7 years), there were no significant differences in PWV between main and control groups. In children aged 8–12 years, the main group was characterized by significantly higher values of maximum PWV compared to healthy peers — 5,1 [4,7–5,8] and 4,6 [4,45–5,05] m/s, respectively (p = 0,041). In group of children with FH aged 13–17 years, compared to the control group, a significant increase in the minimum PWV was observed — 4,7 [4,1–5,1] and 3,9 [3,5–4,1] m/s, respectively (p = 0,009), average PWV — 5,5 [4,8–6,4] and 4,5 [4,2–4,9] m/s, respectively (p = 0,009), and maximum PWV — 6,2 [5,7–7,55] and 5,4 [5,05–5,6] m/s, respectively (p = 0,007). Correlation analysis in patients with FH showed direct correlation between PWVmin, PWVav and PWVmax with total cholesterol (r = 0,46, r = 0,46 and r = 0,464, respectively, p < 0,001). **Conclusions.** Our study demonstrates an increase in the PWV in the aorta in children with FH compared with healthy peers from 8–12 years of age. There is a further progression of arterial stiffness with an increase in the minimum, average and maximum PWV most significant in the group of 13–17 years.

Key words: familial hypercholesterolemia, arterial stiffness, pulse wave velocity, children

For citation: Galimova LF, Sadykova DI, Slastnikova ES, Marapov DI. Change in the aortic pulse wave velocity in children with familial hypercholesterolemia. Arterial'naya Gipertenziya = Arterial Hypertension. 2020;26(6)):640–647. ***doi:10.18705/1607-419X-2020-26-6-640-647***

Изменение скорости пульсовой волны в аорте у детей с семейной гиперхолестеринемией

Л. Ф. Галимова [1, 2], Д. И. Садыкова [2], Е. С. Сластникова [2], Д. И. Марапов [2, 3]

[1] Государственное автономное учреждение здравоохранения «Детская республиканская клиническая больница», Казань, Россия
[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Казанский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Казань, Россия
[3] Учебно-методический центр «Бережливые технологии в здравоохранении», Казань, Россия

Контактная информация:
Галимова Лилия Фаридовна,
ФГБОУ ВО Казанский ГМУ Минздрава России,
ул. Бутлерова, д. 49, Казань, Россия, 420012.
E-mail: lilu1@inbox.ru

Статья поступила в редакцию 06.04.20 и принята к печати 28.08.20.

Резюме

Актуальность. Семейная гиперхолестеринемия (СГХС) — генетическое заболевание, характеризующееся повышением в организме уровня общего холестерина и липопротеинов низкой плотности уже с детства. Изучение связи ранней сосудистой дисфункции с гиперхолестеринемией является важным вопросом, поскольку эти отклонения предшествуют атеросклерозу. **Цель исследования** — оценить жесткость артерий у детей с гетерозиготной СГХС путем измерения скорости пульсовой волны (СПВ) в аорте. **Материалы и методы.** В исследовании участвовали 118 детей. Из них 60 здоровых детей составили контрольную группу и 58 детей с диагнозом гетерозиготная СГХС вошли в основную. Обе группы были разделены на 3 возрастные подгруппы: от 5 до 7 лет, от 8 до 12 лет и от 13 до 17 лет. Диагноз СГХС выставляли в соответствии с Британскими критериями Simon Broome. Всем детям определяли липидный профиль, проводили суточное мониторирование артериального давления с оценкой минимальной, средней и максимальной СПВ (СПВмин, СПВср, СПВмакс) в аорте осциллометрическим методом. **Результаты.** В младшей возрастной подгруппе (5–7 лет) не было выявлено статистически значимых различий СПВ между детьми основной и контрольной групп. У детей в возрасте 8–12 лет основная группа характеризовалась статистически значимо более высокими значениями максимальной СПВ по сравнению со здоровыми сверстниками — 5,1 [4,7–5,8] и 4,6 [4,45–5,05] м/с соответственно ($p = 0,041$). В группе детей с СГХС в возрасте 13–17 лет относительно показателей контрольной группы отмечалось статистически значимое увеличение минимальной СПВ — 4,7 [4,1–5,1] и 3,9 [3,5–4,1] м/с соответственно ($p = 0,009$), средней СПВ — 5,5 [4,8–6,4] и 4,5 [4,2–4,9] м/с соответственно ($p = 0,009$) и максимальной СПВ — 6,2 [5,7–7,55] и 5,4 [5,05–5,6] м/с соответственно ($p = 0,007$). Корреляционный анализ у пациентов с СГХС выявил прямые связи СПВмин, СПВср и СПВмакс с общим холестерином ($r = 0,46$, $r = 0,46$ и $r = 0,464$ соответственно, $p < 0,001$). **Заключение.** Исследование демонстрирует увеличение максимальной СПВ в аорте у детей с СГХС по сравнению со здоровыми сверстниками начиная с 8–12 летнего возраста. Отмечается дальнейшее прогрессирование артериальной жесткости с увеличением СПВмин, СПВср и СПВмакс, наиболее значимое в группе 13–17 лет. Полученная взаимосвязь между уровнем холестерина, возрастом и показателями артериальной жесткости при СГХС позволяет рекомендовать исследование СПВ в качестве возможного дополнительного метода изучения сердечно-сосудистого риска у детей и оценки прогрессирования заболевания.

Ключевые слова: семейная гиперхолестеринемия, артериальная жесткость, скорость пульсовой волны, дети

Для цитирования: Галимова Л. Ф., Садыкова Д. И., Сластникова Е. С., Марапов Д. И. Изменение скорости пульсовой волны в аорте у детей с семейной гиперхолестеринемией. Артериальная гипертензия. 2020;26(6):640–647. ***doi:10.18705/1607-419X-2020-26-6-640-647***

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) 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 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 quitewidespread 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.

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.

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 FH was established in accordance with the British Simon Broome criteria [31]. Th e 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, hypertension, obesity. Written informed consent was obtained from all the participants of the study.

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 examina-

Table 1

CLINICAL AND LABORATORY CHARACTERISTICS OF CHILDREN OF THE MAIN AND CONTROL GROUPS

	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)
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

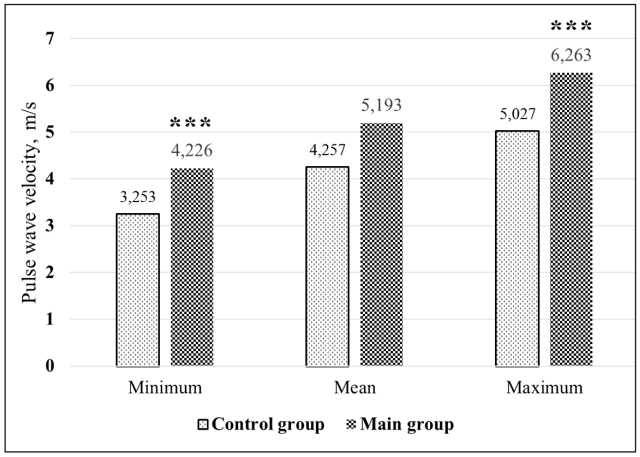
Note: TC — total cholesterol; LDL — low density lipoprotein; HDL — high density lipoprotein; TG — triglycerides.

tion, 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].

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 $p < 0.05$.

Figure 1. Comparison of the values of the pulse wave velocity in the main and control groups



Note: *** — $p < 0.001$.

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,

Table 2

COMPARISON OF THE VALUES OF THE PULSE WAVE VELOCITY DEPENDING ON THE AGE OF THE CHILDREN

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

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

Table 4

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.

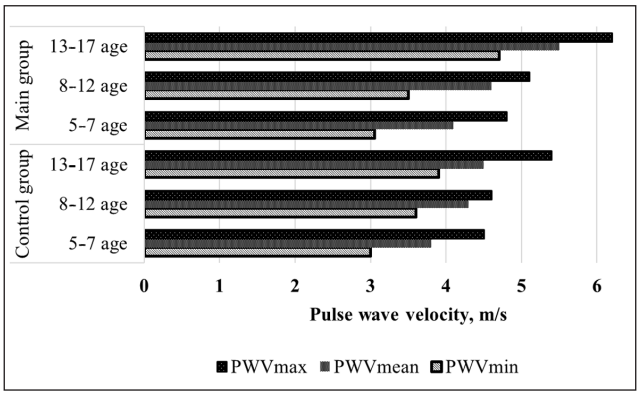
Table 3

INDICATORS OF THE PULSE WAVE VELOCITY OF CHILDREN OF THE MAIN GROUP

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**

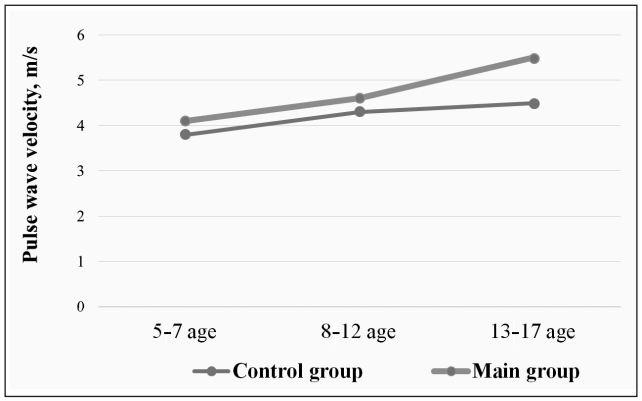
Note: p is the level of significance of the differences.

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, PWV — mean pulse wave velocity, PWVmax — maximum pulse wave velocity.

Figure 3. Dynamics of the increase in the mean pulse wave velocityin the main and control groups, depending on the age of the children



Note: * — p = 0.009.

= 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). 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).

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 FHC (Figure 3).

Taking into account the presence of dyslipidemia in patients with FHC 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).

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 FHC 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 FHC, 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 FHC 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 FHC, 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], elevated body mass index [38, 39]. In the present study, special attention was paid to patients with FHC 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].

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.

Authors declare no conflict of interest.

Conflict of interest

The authors declare no conflict of interest.

References

1. Clinical guidelines. Familial hypercholesterolemia. 2018. Electronic source. URL: https://noatero.ru/sites/default/files/proekt_klinicheskie_rekomendacii_sghs_mz_rf_18.01.pdf. In Russian.

2. Borén J, Chapman MJ, Krauss RM, Packard CJ, Bentzon JF, Binder C et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2020;41(24):2313–2330. doi:10.1093/eurheartj/ehz962

3. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L et al. ESC Scientific Document Group, 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2020;41(1):111–188. doi:10.1093/eurheartj/ehz455

4. De Backer G, Besseling J, Chapman JG, Hovingh GK, Kastelein JJ, Kotseva K et al. Prevalence and management of familial hypercholesterolaemia in coronary patients: an analysis of EUROASPIRE IV, a study of the European Society of Cardiology. Atherosclerosis. 2015;241(1):169–175. doi:10.1016/j.atherosclerosis.2015.04.809

5. Vallejo-Vaz AJ, Kondapally Seshasai SR, Cole D, Hovingh GK, Kastelein JJ, Mata P et al. Familial hypercholesterolaemia: a global call to arms. Atherosclerosis. 2015;243(1):257–259. doi:10.1016/j.atherosclerosis.2015.09.021

6. Pećin I, Hartgers ML, Hovingh GK, Dent R, Reineret Z. Prevention of cardiovascular disease in patients with familial hypercholesterolaemia: the role of PCSK9 inhibitors. Eur J Prev Cardiol. 2017;24(13):1383–401. doi:10.1177/2047487317717346

7. Yezhov MV, Bliznyuk SA, Tmoyan NA, Rozhkova DV, Duplyakov VA, Salchenko MA et al. Register of patients with familial hypercholesterolemia and patients of very high cardiovascular risk with lipid-lowering therapy underperformance (RENESSANS). Russ J Cardiol. 2019;5:7–13. doi:10.15829/1560-4071-2019-5-7-13. In Russian.

8. Vallejo-Vaz AJ, Akram A, Cole D, Watts GF, Hovingh GK et al. Pooling and expanding registries of familial hypercholesterolaemia to assess gaps in care and improve disease management and outcomes: rationale and design of the global EAS Familial Hypercholesterolaemia Studies Collaboration. Atheroscler Suppl. 2016;22:1–32. doi:10.1016/j.atherosclerosissup.2016.10.001

9. Watts G, Gidding S, Wierzbicki A, Toth PP, Alonso R, Brown WV et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. Inter J Cardiol. 2014;171(3):309–325. doi:1016/j.ijcard.2013.11.025

10. Reiner Ž. Management of patients with familial hypercholesterolaemia. Nat Rev Cardiol. 2015;12(10):565–575. doi:10.1038/nrcardio.2015.92

11. Migliara G, Baccolini V, Rosso A, D'Andrea E, Massimi A, Villari P et al. Familial hypercholesterolemia: a systematic review of guidelines on genetic testing and patient management. Front Public Health. 2017;5:252. doi:10.3389/fpubh.2017.00252

12. Castelli WP. Epidemiology of coronary heart disease: the Framingham study. Am J Med. 1984;76(2A):4–12. doi:10.1016/0002-9343(84)90952-5

13. Liu RS, Dunn S, Grobler AC, Lange K, Becker D, Goldsmith G et al. Carotid artery intima-media thickness, distensibility and elasticity: population epidemiology and concordance in Australian children aged 11–12 years old and their parents. BMJ Open. 2019;9(Suppl 3):23–33. doi:10.1136/bmjopen-2017-020264

14. White D, Place R, Michael T, Hoffman E, Gordon PM, Visich P. The relationship between coronary artery disease risk factors and carotid intima-media thickness in children. J Pediatrics. 2017;190:38–42. doi:10.1016/j.jpeds.2017.07.034

15. Marcon D, Tagetti A, Fava C. Subclinical organ damage in children and adolescents with hypertension: current guidelines and beyond. High Blood Press Cardiovasc Prev. 2019;26(5):361–373. doi:10.1007/s40292-019-00345-1

16. Böhm B, Oberhoffer R. Vascular health determinants in children. Cardiovasc Diagn Ther. 2019;9(Suppl 2):S 269–S 280. doi:10.21037/cdt.2018.09.16

17. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. J Am Coll

Cardiol. 2002;39(2):257–265. doi:10.1016/s0735-1097(01)01746-6

18. Plana N, Rodríguez-Borjabad C, Ibarretxe D, Ferré R, Feliu A, Caselles A et al. Lipid and lipoprotein parameters for detection of familial hypercholesterolemia in childhood. The DECOPIN Project. Clin Investig Arterioscler. 2018;30(4):170–178. doi:10.1016/j.arteri.2017.12.003

19. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR et al. American Heart Association Council on Hypertension. Recommendations for improving and standardizing vascular research on arterial stiffness. A Scientific Statement from the American Heart Association. J Hypertension. 2015;66(3):698–722. doi:10.1161/HYP.0000000000000033

20. Cecelja M, Chowienczyk P. Role of arterial stiffness in cardiovascular disease. JRSM Cardiovasc Dis. 2012;1(4):pii: cvd.2012.012016. doi:10.1258/cvd.2012.012016

21. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol. 2005;25(5):932–943. doi:10.1161/01.ATV.0000160548.78317.29

22. Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. Hypertens Res. 2002;25(3):359–364. doi:10.1291/hypres.25.359

23. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension. 2001;37(5):1236–1241. doi:10.1161/01.HYP.37.5.1236

24. Lioufas N, Pedagogos E, Hawley C, Pascoe E, Elder G, Badve S et al. Aortic Calcification and arterial stiffness burden in a chronic kidney disease cohort with high cardiovascular risk: baseline characteristics of the impact of phosphate reduction on vascular end-points in chronic kidney disease trial. Am J Nephrol. 2020;51(3):201–215. doi:10.1159/000505717

25. Feng S, Wang H, Yang J, Hu X, Wang W, Liu H et al. Kidney transplantation improves arterial stiffness in patients with end-stage renal disease. Int Urol Nephrol. 2020;52(5):877–884. doi:10.1007/s11255-020-02376-3

26. Petrák O, Češka R. Vascular age. Vnitr Lek. 2020;65(12):770–774.

27. Ravikumar R, Deepa R, Shanthirani C, Mohan V. Comparison of carotid intima-media thickness, arterial stiffness, and brachial artery flow mediated dilatation in diabetic and nondiabetic subjects (The Chennai Urban-Population Study [CUPS-9]). Am J Cardiol. 2002;90(7):702–707. doi:10.1016/s0002-9149(02)02593-6

28. Kim HL, Kim SH. Pulse wave velocity in atherosclerosis. Front Cardiovasc Med. 2019;6:41. doi:10.3389/fcvm.2019.00041

29. Vasyuk YuA, Ivanova SV, Shkolnik EL, Kotovskaya YuV, Milyagin VA, Oleynikov VE et al. Consensus of Russian experts on the evaluation of arterial stiffness in clinical practice. Cardiovascular Therapy and Prevention. 2016;15(2):4–19. doi:10.15829/1728-8800-2016-2-4-19. In Russian.

30. Vallée A, Cinaud A, Protogerou A, Zhang Y, Topouchian J, Safar ME et al. Arterial stiffness and coronary ischemia: new aspects and paradigms. Curr Hypertens Rep. 2020;22(1):5. doi:10.1007/s11906-019-1006-z

31. Neil HA, Hammond T, Huxley R, Matthews DR, Humphries SE. Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: prospective registry study. Br Med J. 2000;321(7254):148. doi:10.1136/bmj.321.7254.148

32. The indices estimated by the Vasotens® technology in brief. URL: http://vasotens.ru. In Russian.

33. Reiner Z, Simental-Mendía L, Ruscica M, Katsiki N, Banach M, Al Rasadi K et al. Pulse wave velocity as a measure of arterial stiffness in patients with familial hypercholesterolemia: a systematic review and meta-analysis. Arch Med Sci. 2019;15(6):1365–1374. doi:10.5114/aoms.2019.89450

34. Erolu E, Akalın F, Çetiner N, Şaylan Çevik B. Aortic elasticity and carotid intima-media thickness in children with mitral valve prolapse. Cardiol Young. 2017;28(2):292–301. doi:10.1017/s1047951117001950

35. Blain H, Sinaii N, Zeltser D, Lyssikatos C, Belyavskaya E, Keil M et al. Aortic pulse wave velocity in children with Cushing syndrome: a window into a marker of early cardiovascular disease. Endocrinol Diabetes Metab. 2019;2(2):e00054. doi:10.1002/edm2.54

36. Tran A, Burkhardt B, Tandon A, Blumenschein S, van Engelen A, Cecelja M et al. Pediatric heterozygous familial hypercholesterolemia patients have locally increased aortic pulse wave velocity and wall thickness at the aortic root. Int J Cardiovasc Imaging. 2019;35(10):1903–1911. doi:10.1007/s10554-019-01626-5

37. Thurn D, Doyon A, Sözeri B, Bayazit AK, Canpolat N, Duzova A. Aortic pulse wave velocity in healthy children and adolescents: reference values for the vicorder device and modifying factors. Am J Hypertens. 2015;28(12):1480–1488. doi:10.1093/ajh/hpv048

38. Reusz GS, Cseprekal O, Temmar M, Kis É, Cherif AB, Thaleb A et al. Reference values of pulse wave velocity in healthy children and teenagers. Hypertension. 2010;56(2):217–224. doi:10.1161/hypertensionaha.110.152686

39. Doyon A, Kracht D, Bayazit AK, Deveci M, Duzova A, Krmar RT et al. Carotid artery intima-media thickness and distensibility in children and adolescents: reference values and role of body dimensions. Hypertension. 2013;62(3):550–556. doi:10.1161/hypertensionaha.113.01297

40. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: a report of the American College of Cardiology / American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1082–e1143. doi:10.1161/CIR.0000000000000625

41. Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E et al. 20-year follow-up of statins in children with familial hypercholesterolemia. New Engl J Med. 2019;381(16):1547–1556. doi:10.1056/nejmoa1816454

Author information

Liliia F. Galimova, MD, PhD, Republican Children's Hospital, ORCID: 0000–0001–5576–5279, e-mail: lilu1@inbox.ru;

Dinara I. Sadykova, MD, PhD, DSc, Head, Department of Hospital Pediatrics, Kazan State Medical University, ORCID: 0000–0002–6662–3548, e-mail: sadykovadi@mail.ru;

Eugenia S. Slastnikova, MD, PhD Student, Department of Hospital Pediatrics, Kazan State Medical University, ORCID: 0000–0002–1732–7443, e-mail: e.slastnikova@mail.ru;

Damir I. Marapov, MD, PhD, Assistant, Educational and Methodical Center "Economical Technologies in Healthcare", Kazan State Medical University, ORCID: 0000-0003-2583-0599, e-mail: damirov@list.ru.