Assessment of arterial stiffness in Marfan syndrome and marfanoid phenotype

Ocena sztywności tętnic w zespole Marfana i fenotypie marfanoidalnym

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Abstract

Introduction. Marfan syndrome is a hereditary connective tissue disorder caused by impaired synthesis of a fibrillin protein. This results in a broad spectrum of clinical manifestations, in particular cardiovascular, skeletal and ocular features. Marfanoid phenotype is defined as manifesting some features of Marfan syndrome, but not fulfilling the criteria of the diagnosis. Abnormal synthesis of the fibrillin is the reason of impairment of elastic fibers. This effects in increasing arterial stiffness, which can be characterized by pulse wave velocity (PWV) and augmentation index (AI).
Material and methods. Study included 72 patients suspected of Marfan syndrome. On the basis of modified Ghent criteria they were divided into two groups: 37 patients were diagnosed with Marfan syndrome and 35 patients were classified as marfanoid phenotype. Research included also 36 healthy controls. PWV and AI values were obtained by applanation tonometry method.
Results. Mean PWV is higher in Marfan syndrome rather than marfanoid phenotype and healthy controls. The lowest mean value of PWV was found among patients with marfanoid phenotype. The highest mean AI value was presented in Marfan syndrome. The lowest mean AI was obtained in a group with marfanoid phenotype.
Conclusions. Patients with Marfan syndrome are presenting higher values of PWV and AI than patients with marfanoid phenotype or healthy controls. The lowest values of PWV and AI were obtained among patients with marfanoid phenotype. Patients like these are taller than the others, however, their arterial walls most likely have correct structure, which causes beneficial hemodynamic conditions.
Key words: Marfan syndrome, marfanoid phenotype, arterial stiffness, pulse wave velocity, augmentation index, applanation tonometry

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Streszczenie

Wstęp. Zespół Marfana jest uwarunkowaną genetycznie chorobą tkanki łącznej spowodowaną nieprawidłową syntezą białka fibryliny. U chorych występuje wiele objawów klinicznych, zwłaszcza wiązanych z układem sercowo-naczyniowym, szkieletem i narządem wzroku. Fenotyp marfanoidalny definiuje się jako występowanie niektórych cech zespołu Marfana, jednak niespełniających kryteriów rozpoznania tego zespołu. Nieprawidłowa synteza fibryliny powoduje zaburzenia struktury włókien elastycznych. To prowadzi do zwiększenia sztywności tętnic, którą można mierzyć za pomocą szybkości fali tętna (PWV, *pulse wave velocity*) i wskaźnika wzmocnienia (AI, *augmentation index*).

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Materiał i metody. Do badania włączono 72 chorych z podejrzeniem zespołu Marfana. Na podstawie zmodyfikowanych kryteriów Ghenta chorych podzielono na dwie grupy: u 37 osób rozpoznano zespół Marfana, a u 35 stwierdzono fenotyp marfanoidalny. W badaniu uwzględniono ponadto grupę kontrolną złożoną z 36 zdrowych osób. Wartości PWV i AI uzyskano metodą tonometrii aplanacyjnej.
Wyniki. Średnia wartość PWV była wyższa u osób z zespołem Marfana niż w grupie z fenotypem marfanoidalnym i w grupie kontrolnej. Najniższą wartość PWV stwierdzono u osób z fenotypem marfanoidalnym. Najwyższą średnią wartością AI cechowała się grupa z zespołem Marfana, natomiast najniższą — osoby z fenotypem marfanoidalnym.
Wnioski. U chorych z zespołem Marfana wartości PWV i AI były wyższe niż u osób z fenotypem marfanoidalnym i zdrowych osób z grupy kontrolnej. Najniższe wartości PWV i AI stwierdzono u osób z fenotypem marfanoidalnym. Chorzy ci są wyżsi niż pozostali, jednak w ich przypadku ściany tętnic mają zwykle prawidłową budowę, co zapewnia korzystne warunki hemodynamiczne.
Słowa kluczowe: zespół Marfana, fenotyp marfanoidalny, sztywność tętnic, szybkość fali tętna, wskaźnik wzmocnienia, tonometria aplanacyjna

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Introduction

Marfan syndrome is an autosomal dominant connective tissue disorder. In most cases it is caused by a mutation of fibrillin 1, a protein which is essential for the formation of elastic fibers [1–3]. It appears 4–6 times per 100 000 cases, usually in families [4]. In consequence of the mutation various clinical manifestations are present, primarily skeletal, cardiovascular and ocular [1, 3]. Characteristic feature of this syndrome is the wide spectrum of phenotypic changes [2]. The relationship between the type of mutation and clinical phenotype has been demonstrated [2, 4]. In this research, marfanoid phenotype was defined as a clinical circumstance where a patient presents some of the Marfan symptoms, however he does not fulfill the criteria needed to proper diagnosis [2].

Alteration in organisation of the elastin fibers, apart from resulting in characteristic clinical features, causes changes in the structure of arterial walls. Representative image of this is a damage of those fibers in intima media while the mucopolysacharides are deposited in their place, which contributes to the reduction of arterial wall susceptibility and thus to the increase of their stiffness [3, 5–8]. This applies in particular to the elastic arteries- the aorta and its major branches. The impairment of the vascular wall increases the probability of pathological dilation of the arteries and the most serious complications of Marfan syndrome — aortic aneurysm or aortic dissection [9].

Applanation tonometry is a method of pulse wave analysis. It provides information about pulse wave velocity (PWV) and augmentation index (AI). These are the parameters that characterize arterial stiffness [10–13]. This method enables the estimation of the pressure in the aorta (central pressure) and analysis of the pressure curve exerted on the arterial wall. [12, 14] Increase of the arterial stiffness results in an increase in pulse wave propagation velocity. The importance of PWV measure for cardiovascular risk assessment has been previously demonstrated [10, 12, 14, 15]. The feature that implements those processes is the event of reflected wave of pressure spreading to peripheral vascular bed and its return to heart. This reflected wave begins in places of division of arteries. In proper conditions, the reflected wave returns to the heart during diastole, which increases diastolic blood pressure and improves coronary flow. In case of increased arterial stiffness, the return of reflected wave occurs too quickly — at the time of contraction. This results in an increase in systolic central blood pressure and pulse pressure (PP) thus the difference between systolic and diastolic blood pressure [10, 14]. The above described mechanism leads to development of hypertension. The lack of physiological coronary flow during diastole is also an important part of this phenomenon. A factor that characterizes the degree of increase in the aortic pressure during systole is the augmentation index [12, 14, 16]. It is defined as quotient of gain factor (difference between pressure created by heart in the moment of systole and actual pressure in the aorta) to the pressure in aorta. It assumes positive values in case of increased arterial stiffness, when the reflected wave increases central systolic pressure. Negative values represent the physiological situation and therefore the return of the reflected wave at diastole [12, 14].

Increased arterial stiffness in Marfan syndrome was previously demonstrated [3, 5–9, 11, 17, 18]. It is also essential to evaluate the occurrence of

increased arterial stiffness in patients who do not fulfill all diagnostic criteria for Marfan syndrome, but absorb clinician attention due to characteristic phenotype. It is not excluded that such patients also have an increased risk of cardiovascular disease.

The aim of the study was to assess arterial stiffness in patients with Marfan syndrome and marfanoid phenotype.

Material and methods

The study included 76 patients aged 6 to 64 years, referring to the clinic with suspicion of Marfan syndrome. All of the patients gave conscious written consent to take part in this research. In order to make a correct diagnosis, they have been examined on different specific spheres. Each patient was subjected to cardiological, orthopedic and ophthalmic examination taking into account modified Ghent from 2010 [19]. The patients were divided into two groups — patients who met criteria were diagnosed with Marfan syndrome (40 patients) and the remaining patients were classified as patients with marfanoid phenotype (36 patients).

PWV analysis excluded patients with ventricular (3 patients) and supraventricular (1 patient) arrhythmias. Finally, 37 patients with Marfan syndrome and 35 patients with marfanoid phenotype were included in the analysis. 36 healthy subjects were also included in the research as a control group (Table I).

Blood pressure measurement

The examination was performed after a 5-minute rest in a sitting position. Initially, the blood pressure was measured by sphygmomanometer. Measurements were made twice on each arm at 1–2 minute intervals. Values obtained from each upper limb were averaged. As a final value, the highest from upon average values was assumed (Table II).

Measurement of pulse wave velocity and central pressure

After measuring the peripheral pressure, the PWV was measured. The examination was performed in the same room where the patient was lying on his back. The COMPLIOR® sensors were located in the place of the most perceptible pulse over the carotid and femoral arteries. The distance between the sensors was measured with measuring tape. After registering a sufficient number of heart cycles, registration was stopped. For pulse waveform analysis, COMPLIOR® System V1.9 was used. The system calculated the PWV value based on the distance between the sensors and the time needed to move the pulse wave between them. In this way, a total of three PWV measurements were made. In each measurement, the position of the sensors remained unchanged. Therefore, the time needed to move the pulse wave was the discriminating parameter. From the obtained values, the mean PWV was calculated for each patient group based on the formula:

$$(PWV_1 + PWV_2 + PWV_3) / 3 = PWV_{mean}$$

COMPLIOR® Analyse software at the time provides information about central pressure. It is counted on the bases of analyses of pulse wave from the carotid sensor. Al index (amplification index) was used in the research, on the bases of central pressure. Measurement of PWV and AI was made by 4 researchers.

Statistical analyses

Studied parameters were presented as average values ± standard deviation. The importance of differences between each group was measured by U-Mann-Whitney test. Statistically important values were estimated to be $p < 0.05$. Statistical analyses were made in STATISTICA 12.5 software.

Table I. Subject characteristic

	Marfan syndrome	Marfanoid phenotype	Control group
Number of patients	37	35	36
Women	16 (43%)	18 (51%)	21 (58%)
Men	21 (57%)	17 (49%)	15 (42%)
Age (years)	25 ± 14	19 ± 8	22 ± 6
Height [cm]	176 ± 18	175 ± 14	173 ± 15
Weight [kg]	63.70 ± 19.40	56.39 ± 15.14	77.49 ± 38.66
BMI	20.14 ± 5.62	18.19 ± 3.45	26.25 ± 13.01

BMI — body mass index

Table II. Peripheral blood pressure in each group

	Marfan syndrome	Marfanoid phenotype	Control group
SBP [mm Hg]	120 ± 15	113 ± 12	119 ± 13
DBP [mm Hg]	74 ± 11	68 ± 7	74 ± 8
PP [mm Hg]	52 ± 31	44 ± 10	45 ± 13
MAP [mm Hg]	89 ± 11	83 ± 8	89 ± 8

SBP — systolic blood pressure, DBP — diastolic blood pressure, PP — pulse pressure, MAP — mean arterial pressure

Table III. Pulse wave velocity in each group

	Marfan syndrome	Marfanoid phenotype	Control group
PWV [m/s]	6.34 ± 1.76	5.54 ± 1.31	6.02 ± 3.56
Range [m/s]	4.00–12.47	3.50–10.73	3.50–18.10
Median value	6.25	5.53	5.63

PWV — pulse wave velocity

Table IV. P values for PWV results in each group

	Marfan syndrome	Marfanoid phenotype	Control group
Marfan syndrome	—	0.0110	NS
Marfanoid phenotype	0.0110	—	NS
Control group	NS	NS	—

NS — non significant

Table V. Augmentation index values in each group

	Marfan syndrome	Marfanoid phenotype	Control group
AI (%)	–4.49 ± 23.53	–19.60 ± 25.45	–18.22 ±17.22
Range	(–54.2)–63.06	(–63.33) –66.41	(–48,6) –21.03
Median value	–3.42	–19.61	–21.57
AI > 0 (number of patients)	14 (37.8%)	5 (14.3%)	7 (19.4%)

AI — augmentation index

Results

The results of PWV measurements were showed in Table III. Statistically significant difference in the value of PWV was found between the groups of patients with Marfan syndrome and patients with marfanoid phenotype. The referential value of PWV according to European Society of Hypertension was exceeded by 2 (5.4%) patients in a group with Marfan syndrome, 2 (5.7%) patients in a group with marfanoid phenotype and 3 (8.3%) patients in a control group. Because of low average age in all of studied groups, another reference value was taken into account, according to data published in 2015 [10]. It equals 6.2 m/s for patients aged less than 30 years old. This value was exceeded by 19 (51.4%) patients in a group with Marfan syndrome, 11 (31.4%) patients in a group with marfanoid phenotype and 14 (38.9%) patients in a control group (Table IV).

The highest median value of PWV was presented between patients with Marfan syndrome, lowest one between patients with marfanoid phenotype. In Marfan group was obtained the narrowest range of PWV values in comparison with remaining groups.

The results of amplification index measurements were presented in Table V. Statistically significant difference was found between Marfan syndrome and marfanoid groups and between Marfan group and control group. The highest average value of AI was presented in a group with Marfan syndrome and the lowest average value was obtained in a group with marfanoid phenotype. However, in marfanoid group the range of AI values was very wide (Table VI).

Table VI. P values for AI results in each group

	Marfan syndrome	Marfanoid phenotype	Control group
Marfan syndrome	—	0.0030	0.0071
Marfanoid phenotype	0.0030	—	NS
Control group	0.0071	NS	—

NS — non significant

Discussion

The results of the research prove previously demonstrated principle that due to altered structure of the elastic fibers, arterial walls among patients with Marfan syndrome have reduced susceptibility thus increased stiffness [5–9, 11, 17, 22]. This expresses in increased pulse wave velocity in comparison to healthy controls and to patients representing marfanoid phenotype. Mean PWV value was the highest amidst patients with Marfan syndrome. After taking into account another reference value for PWV measurement [10] given in publication value 6.2 m/s exceeded 19 patients in Marfan group, which represents 51.4% of the group. This is at the same time the highest percentage of values exceeding reference value. It can be considered as probable that PWV among these patients would subsequently increase over time. Finally the majority of them will most likely exceed the reference value deriving from European Society of Hypertension (ESH) recommendations — 10 m/s, which was previously recognized as a sign of increased cardiovascular risk and presence of subclinical organ damage deriving from hypertension [10, 14, 15]. Considering this patients with Marfan syndrome should be involved in periodic examinations aiming to assess PWV value [20]. The gold standard for this according to ESH is the assessment of carotid-femoral pulse wave velocity by applanation tonometry [15].

In conducted analysis the PWV values obtained in the marfanoid phenotype group were lower than the values received in Marfan group and also in control group. It applies to both average and median value of PWV. Statistically significant difference was found in both PWV and AI values between patients with Marfan syndrome and marfanoid phenotype. It indicates significantly more frequent occurrence of increased arterial stiffness among patients fulfilling diagnostic criteria for this syndrome.

In this study patients with marfanoid phenotype were characterized by the lowest values of systolic and diastolic blood pressure and the lowest value of pulse pressure. It suggests low degree of systolic blood pressure augmentation deriving from pulse wave return. In control group obtained peripheral blood pressure values were different — both systolic and diastolic blood pressure were higher than in marfanoid group, but similar to values obtained in Marfan group.

Another factor describing arterial stiffness is an amplification index [11, 12, 14, 16, 17]. According to research, it strongly correlates with the value of PWV. It reflects the percentage of increase or decrease in aortic stiffness in result of arrival of the waves reflected on the circuit to the heart. As a result of calculation method, this factor is independent of blood pressure [12]. In our analysis, AI in a group with patients with Marfan syndrome was significantly higher than in the other group. This proves higher amplification pressure than in other groups in a moment of ventricular contraction this demonstrates that higher ventricular pressure during ventricular contraction and higher disturbance of ventricular wall properties in response to reflected wave is higher than in other groups. The mean value obtained in patients with Marfan syndrome is negative. The range of results received in this group was wide. In addition, among 37 patients in this group, positive AI values were obtained in 14 patients, representing 37.8% of the group, compared with 14.3% in the marfanoid group and 19.4% in the control group.

This shows the highest incidence of haemodynamically disadvantageous situation — too early return of reflected wave in group with patient with Marfan syndrome. In the group of patients with marfanoid phenotype, the amplification coefficient assumed a wide range of values, with the most negative mean of all results and the smallest proportion of patients receiving a positive value. This indicates the most favorable hemodynamic conditions among all studied patient groups [14]. The AI reference values have not yet been determined. It can therefore be assumed that in our study in a group with patients with marfanoid phenotype, the obtained values of the central pressure amplification index showed lower arterial stiffness than those of Marfan syndrome and control patients.

PWV measurement methods are constrained by operator dependency and poor reproducibility of results [12, 13]. The value of PWV and AI is influenced by a number of other factors, height, gender,

blood pressure, vascular resistance, ejection volume, pulse waveform, heart rate, smoking or vasomotor tension. For this reason, and because of the limitations of the statistical analysis resulting from the low abundance of the study groups, it would be advisable to repeat the PWV and AI measurements on the larger groups in terms of abundance.

The obtained results suggest that patients with marfanoid phenotype have better arterial susceptibility both from patients with Marfan syndrome and those in the control group. Marfanoid patients draw the attention of their physician with their distinctive appearance — tall, slim figure and phenotypic features reminiscent of patients with Marfan syndrome [1, 2, 4]. Despite this, they have better haemodynamic parameters than patients from other groups. This is probably due to their higher growth and lower BMI (body mass index) relative to the rest of the population while maintaining a normal histological structure of the arterial walls [21].

Conclusions

Patients with Marfan syndrome have higher vascular stiffness, which is expressed by higher pulse wave velocity and higher central pressure augmentation index than in patients with marfanoid phenotype and in the control group.

In patients with marfanoid phenotype, the lowest values of systolic and diastolic blood pressure and pulse pressure were observed. Both the pulse wave velocity and the amplification factor in this group were among the lowest among all subjects.

It would be advisable to carry out a study in a larger group of patients with a marfanoid phenotype to confirm the observed haemodynamic properties in this population.

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