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Pulse wave velocity and central aortic pressure in obese children according to the non-invasive arteriography results

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The article presents information value of non-invasive arteriography, which reveals early signs of cardiovascular pathology formation in children, using a large number of trials in children. The authors examined predictors of cardiovascular catastrophes' development, confirmed in adults: aortic wall's stiffness, central aortic pressure and pulse pressure – that have not been sufficiently studied in children yet. The article shows that the high-technology method of non-invasive arteriography allows revealing changes of these parameters in children on the preclinical stage. It also shows their correlation with body mass index, fatty hepatosis, direct correlation of weight gain with connection of pulse wave velocity and central blood pressure and importance of follow-up evaluation of these parameters. Heterogeneity of the group of obese children in terms of these parameters is a premise for development of individual approach to control and prevention of cardiovascular complications' development risk in childhood.
Keywords: *arteriography, aortic wall's stiffness, pulse wave velocity, obesity, prevention, predictors, cardiovascular alterations, children.*

INTRODUCTION

The integrated cardiovascular continuum concept, i.e. the continuous development of cardiovascular diseases (from risk factors to the development of chronic cardiovascular collapse), has recently been formed in cardiology. Unfortunately, preventive cardiology has not obtained sufficient application in our country, which is why it is no wonder that Russia takes one of the leading positions in the world in mortality of cardiovascular diseases [1, 2]. Mortality of cardiovascular diseases takes 56% of the total mortality; arterial hypertension (AH) is observed in 1/3 of the adult population [3]. According to the population studies conducted in Russia, AH rate among children and adolescents is 2-18% and is continuously increasing; arterial hypertension is also often asymptomatic [4, 5, 6]. Considerable arterial hypertension spread among children of 13-15 years of age and difficulty of correcting the high arterial pressure (AP) in puberty, hereditary factor and pernicious habits contribute to the disease formation [7]. One of the other most serious issues of public health all over the world in the XXI century is obesity. It is estimated that at least 22 mn children under 5 years of age were overweight [8]. Obesity, atherosclerosis, arterial hypertension and diabetes are closely interconnected, start in childhood and steadily increase the rate of mortality of cardiovascular diseases. This is why there is an urgent need in revealing early markers of the future cardiovascular catastrophes as early as on the preclinical stage in childhood. Automated machines are lately being used to evaluate new hemodynamic parameters. Having indisputable significance for diagnosing arterial pressure disorders, the traditional Korotkov AP measurement method is considerably complemented by new parameters, which allow changing the approach to diagnostics and arterial hypertension treatment (in a sense). Establishment of accessible equipment and easy-to-use arteriography served as an impulse for the development of arterial rigidity study and, therefore, of new independent predictors of the development of life-threatening cardiovascular complications, such as stroke and heart attack, in the adult population. Thus, great attention is given to the study of aortic wall elasticity, central arterial pressure (CAP) and pulse pressure (PAP), which indirectly reflect condition of the whole cardiovascular system. Pulse wave velocity (PWV) is the classic marker of arterial rigidity/elasticity of great vessels [9-11].

The results of numerous trials in adults, which confirmed that PWV, CAP level and augmentation index are the factors significantly affecting prognosis in the patients with AH, served as weighty arguments for the inclusion of these indicators in the list of the parameters tested when selecting anti-hypertension therapy and searching for the subclinical lesion of target organs at AH in adults (Workgroup of the European Society of Hypertension, 2010) [13]. This area of study has not obtained sufficient development for pediatrics yet. In recent years, a new non-invasive arteriography using apparatus TensioMed (Hungary) has been applied; it showed itself to good advantage in terms of application in children (more than 4,000 trials) [14]. An arteriograph registers aortic PWV and such parameters as pulse and central aortic pressure. CAP determines perfusion of internal organs and is the most integrative hemodynamic indicator [15], as it reflects the mean aortic pressure within one cardiac cycle, and depends on cardiac output, peripheral resistance, rigidity of great and average arteries and size of the reflected wave (pic. 1).

The CAP is calculated by means of registering the reflected waves located by the arteriograph's piezoelectric crystal detector situated in the cuff put on a shoulder during complete occlusion of the brachial artery. When aortic wall rigidity increases, the reflected wave is not only absorbed insufficiently, but also returns to the aortic systole due to the pulse wave velocity increase; this causes increase in the CAP and the PAP (pic. 2).

The aim of this study was to attempt to analyze changeability of the PWV and the CAP obtained by means of the non-invasive arteriography method in overweight and obese children.

PATIENTS AND METHODS

We analyzed results of examination of 505 children of 3-17 years of age:

- 246 virtually healthy children (128 girls and 118 boys) with neither complaints nor clinical symptoms of a cardiovascular system lesion; the body mass index (BMI) and the arterial pressure level were within the age-gender norm [16, 17]. Acute viral infections and children's infectious diseases were prevalent in the anamnesis among the previous diseases. At examination, the pediatrician concluded that the children were virtually healthy. All children denied smoking, although we cannot objectively trust this clause of the anamnesis;
- 259 patients with the altered body weight (99 girls and 160 boys); 8 children out of them were slightly underweight (BMI<-2 SD), 104 – overweight (BMI – 1-2 SD), 107 – obese (BMI>2 SD). According to the hepatic ultrasonic examination undergone by 94 children in that group, 44 had symptoms of fatty hepatosis.

Work with each patient involved anamnesis and anthropometry taking; jugular recess / symphysis (JUG-SY) range measurement; this range is in direct proportion to the distance from aortic origination to its bifurcation. The children were examined by a pediatrician, an endocrinologist, a cardiologist, a gastroenterologist and a neurologist. Additional examination – general blood and urine analysis, biochemical blood analysis (glucose, total cholesterol, lipid composition), abdominal ultrasonic examination – was conducted. We excluded hypothalamic, endocrine and mixed forms of obesity. The main study method – non-invasive (oscillometric) arteriography – was employed using apparatus TensioMed (Hungary). Rest before and during the trial was prerequisite for measurement accuracy. Arterial pressure parameters at the moment of study ought to have corresponded to normal values (thus, we ruled out the "white coat" effect). PWV was registered in all patients. We obtained the CAP parameters arteriographically in 408 patients.

In terms of the statistical data manipulation, due to the insufficient knowledge of non-invasive arteriography parameters in children, first of all, we considered it necessary to emphasize giving exhaustive descriptive statistics, including means of visualizing distributions and interconnections of the indicators. Secondly, we applied Mann-Whitney and Kruskal-Wallis tests to compare level of the parameters in the children under study, e.g., to compare a group with a certain pathology and a group without it. When it was required to exclude exposure to the external variables (e.g., age or sex), the Mann-Whitney test results were checked in the framework of the complex parametric model of dispersion analysis with simultaneous participation of several factors. We present linear correlation coefficients in order to illustrate some of the interconnections. We illustrated the comparison of diagnostic values of a range of indicators with ROC-curve construction. The trial's statistical data were manipulated using package IBM SPSS Statistics 21.

STUDY RESULTS AND DISCUSSION

Spread of CAP and PWV parameters

We analyzed spread of CAP and PWV parameters in all age-sex groups; we united the group of healthy children with the groups of overweight and obese children.

CAP spread was symmetrical; the bulk of observations was concentrated within the range of 85-100 mm Hg (10 percentile – 83; median – 93; 90 percentile – 104). PWV spread gravitated toward the normal values despite having a marked asymmetry due to a small number of increased PWV values (more than 10 m/s) (pic. 3): 10 percentile – 5; median – 5.8; 90 percentile – 7.2. As the further analysis shows, existence of the right "tail" in the PWV spread was connected with different pathologies.

Tb. 1 concludes CAP and PWV (median) spread by age groups and sex. Median evaluation is not reliable for all age groups; however, Kruskal-Wallis test confirms significant CAP and PWV differences between the age groups. In fact, both CAP and PWV slightly increase with age. Median difference is far lower than the range of the values. Sex differences do not reach statistical significance with $\alpha=0.05$.

Correlation of CAP and PWV with weight alteration

In our trial, we revealed correlation of CAP and PWV and BMI in children. Graphical analysis (pic. 4) shows different character of this correlation for CAP and PWV. BMI-CAP correlation ratio is moderate and linear ($r=0.441$; $p<0.001$; see pic. 4a). At the same time, there is almost no BMI-PWV correlation when BMI is less than 22-23; however, when the BMI value increases, PWV starts increasing faster than in a linear progression. Thus, the PWV-BMI correlation bears signs of a quadratic correlation. The character of correlation is partially formed by strong uneven PWV outputs within 10-15 m/s in the group of patients with BMI>24.

There is a similar dynamics for both parameters if we divide children into groups by weight alteration (on the basis of the number of standard BMI alterations). Pic. 5 presents 10, 25, 50, 75 and 90 CAP and PWV percentiles for each weight alteration group. From the groups of the underweight to the groups of the overweight, the percentile CAP lines increase evenly and the differences between percentiles do not become stronger. PWV tendencies are more peculiar: in lower percentiles, the PWV increase from the groups of the underweight to the groups of the overweight is low or even imperceptible at all, while 75 and 90 percentiles demonstrate increase in the number of differences from lower percentiles. This observation may clarify the conjectured character of PWV correlation with excess weight. PWV is not increased in all the examined overweight patients. However, there are subgroups of patients, in which PWV values at excess weight and obesity are rather different from the normal values (probably, due to the non-linear character of PWV-BMI correlation described above).

Different CAP and PWV levels in different weight alteration groups are confirmed by the Kruskal-Wallis test. CAP: $\chi 2=49{,}9$; $df=4$; $p<0.001$. PWV: $\chi 2=10{,}6$; $df=4$; $p<0.031$. As you can see, the PWV data are slightly better than the CAP data and correspond to the conjecture that there are no differences between weight alteration groups. This is probably caused by a different character of PWV increase: not only does the range of PWV values shift, but this range also lengthens towards larger values with transition to excess weight and obesity. Still, this criterion indicates significant differences between the groups in terms of PWV as well.
Given the fact that the obtained data are not well-balanced by age and sex, we decided to evaluate each parameter in the framework of the parametric model of the 3-factor dispersion analysis, which would involve the main sex, age and weight alteration grade effects at the same time, in order to rule out false conclusions on the correlation of CAP and PWV with weight alteration. Age values were organized into 5 groups (refer to tb. 1 about range width and the number of patients in each group). Analysis results in terms of significance of model effects are given in tb. 2. We can see that age affects the CAP and PWV levels significantly; this ought to be considered when developing the relevant norms. The patient's sex is also on the verge of exposure significance in terms of CAP. However, in both cases, when we simultaneously consider sex, age and weight alteration, the latter factor remains significant.

CAP and PWV changes at fatty hepatosis

For a range of patients with altered (excess) weight, the examination results included information on additional pathologies. This section describes correlation of arteriography indicators and fatty hepatosis (diagnosed by an ultrasonic examination).
Tb. 3 shows that many arteriography indicators are sensitive to fatty hepatosis. A group of patients with fatty hepatosis has increased parameters in most arteriography indicators. PWV, SAP, mean AP and CAP reach significant differences (all of them have higher median values at hepatosis than when hepatosis is not present).
Pic. 6 shows that both indicators demonstrate steady shift towards the higher value of the bulk of values despite the CAP and PWV spreads overlap considerably in groups of patients with hepatosis and without it.
If we consider CAP, SAP, mean AP and PWV as diagnostic hepatosis criteria, we may observe that ROC-curves of indicator values are virtually the same (pic. 7). Areas under curves for different parameters have been measured from 0.65 to 0.69 with 95% confidence intervals: from 0.53 (the lowest bottom limit among the values) to 0.8 (the highest upper limit). As we can see, arteriography data may potentially be considered hepatosis predictors (e.g., with 60% specificity, the PWV sensitivity reaches ca. 69%), although it is far from the "gold standard" (ultrasonic examination). More importantly, these empirical data confirm the launch of vascular remodeling processes even in infants with a range of pathologic alterations present (excess weight, lipid metabolism disorder, fatty hepatosis).

PWV and CAP in the setting of hypercholesterolemia

In our trial, we did not reveal correlation of PWV and CAP with cholesterol, its primary fractions and blood glucose.
We revealed signs of weak non-linear correlation of PWV and high-density lipoproteins (HDL, antiatherogenic cholesterol fraction): low HDL values correspond to high PWV values; the higher the HDL, the lower the PWV (pic. 8). However, small amount of data on cholesterol in our trial (42 patients) did not allow confirming existence of this correlation and studying it in better detail.

Structure of correlation of PWV, CAP and other AP parameters

Tb. 4 contains linear correlations of CAP and other arteriography indicators in different weight alteration groups. Positive nature of these correlations may be mentioned. Correlation of CAP and PWV is less close than with pressure indicators.
Although existence of strong positive correlations of CAP and other pressure indicators is expected (it is also obvious that CAP is more closely connected with pressure indicators in the brachial artery), it is interesting to mention the tendency to weaker linear association in the groups of the overweight in comparison with the groups of the underweight. This tendency can be tracked for correlations with all indicators: SAP, DAP, mean and pulse AP. Correlations in the group of the underweight are virtually similar, though they are somewhat “looser” due to the values standing out from the general correlation scheme. These possibly are signs of the system’s imbalance (i.e. miscoordination of normal correlations) at excess weight. The registered CAP in 2 obese patients was higher than the SAP in the brachial artery. Given preservation of elastic features of aortic wall, the CAP level in a healthy person ought to be lower than the AP level in the brachial artery. The so called amplification pressure – the difference between CAP and peripheral AP [18] – is maximal in youth and reduces with age. It depends on the aortic wall’s rigidity, AP level, genetic peculiarities of elastic fibers, collagen rigidity, involution rate of the crucial structural proteins and fibulin [19].
It ought to be mentioned that we did not observe the effect of monotonous linear correlation weakening only in the CAP-PWV couple. As we concentrate on CAP and PWV in this trial, we study the nature of this correlation in more detail (pic. 9). There actually is weak positive association of CAP and PWV values in all weight alteration groups; however, the character of spread of values in the group of the overweight and obese is considerably different from the spread of values in other groups. This group of values is shifted to the right (towards higher levels), CAP axis, and is present on the whole PWV range with considerable output of several dots outside of the general PWV range (more than 7 m/s).
The PWV correlation with other pressure indicators observed in the trial was rather weak (correlation coefficients: SAP – 0.264, DAP – 0.141, mean AP – 0.237, pulse AP – 0.217); however, all correlations are significantly different from zero; $p<0.001$. The correlation may become insignificant in weight alteration subgroups, without apparent regularity of the correlation closeness at the shift from one subgroup to another.
Pathophysiological mechanisms of CAP fluctuations are more difficult than those of the peripheral AP fluctuations, which is traditionally measured in the brachial artery. According to the trials of adult patients with cardiovascular pathology, we revealed that CAP values correlate with the degree of remodeling of great vessels and pulse wave velocity as a classic indicator of the vascular wall’s rigidity [20]. We established that CAP has high prognostic value for risks of development of cardiovascular catastrophes even on the subclinical stage of atherosclerosis development [21] in adults. However, the level of CAP and PAP only poorly correlates with PWV in the children in our trial. The nature of spread of PWV values in the children with altered weight requires additional research. Interestingly, CAP-PAP correlation is weaker in overweight patients than in the groups of the underweight or of the normal weight.

CONCLUSIONS

In this trial we revealed significant correlation of the children’s pulse wave velocity (indicator of vascular remodeling) and BMI. We observed that PWV, along with arterial pressure parameters, has a steady, though weak age dynamics; it is necessary to consider this when selecting arteriography standards in the Russian population of children. Arteriography indicators are not closely associated with hypercholesterolemia; this reconfirms relativity of this criterion as a predictor of atherosclerosis development and vascular disorders in children. At the same time, the obtained data indicate that PWV and central aortic pressure may be predictors not only of vascular remodeling and atherosclerosis, but also of fatty hepatosis in obese children. Thus, the most significant pulse wave velocity increase was observed in the children shifting from the group of the overweight to the group of the obese. According to the trials in adults [22], we distinguished both parameters (CAP and PAP) as independent and separate markers of cardiovascular catastrophes in adults and are the most stable correlates of these conditions in the setting of the increased individual changeability from measurement to measurement of the other AP parameters. The aim of this trial was not analyze pulse pressure in detail. We revealed weak PWV-PAP correlation in children. We observed that the correlation of CAP and peripheral AP weakens with weight gain, while CAP-PWV correlation remains intact; this may indicate initial symptoms of hemodynamic alteration accompanied with vascular remodeling and attract attention to the more detailed study of this parameter in children.

Trial results indicate that arteriography as a convenient and adapted to childhood study method ought to be applied to all overweight children on the outpatient stage of examination. Interestingly, the group of overweight and obese children is heterogeneous in terms of remodeling index alteration degree, character and degree of CAP alteration and, therefore, in terms of prognosis of risk of cardiovascular catastrophes' development. This fact ought to promote development of individual approach to control and prevention of risk of cardiovascular complications on the preclinical stage in as early as childhood.

Table 1. Medians of central arterial pressure (CAP) and pulse wave velocity (PWV) in groups by sex and age

Group		**CAP, mm Hg**		**PWV, m/s**	
		Median	*n*	Median	*n*
Age, years	3-5	92.2	15	5.6	30
	6-8	90.5	135	5.7	161
	9-11	91.6	172	5.9	212
	12-14	100.7	54	6.1	65
	15-17	98.2	32	6.3	37
Kruskal-Wallis test		χ^2=47, *df*=4, *p*<0.001		χ^2=34, *df*=4, *p*<0.001	
Sex	Girls				
	Boys				
Kruskal-Wallis test		χ^2=1.7, *df*=1, *p*=0.196		χ^2=2.0, *df*=1, *p*<0.149	

Table 2. Results of dispersion analysis for central arterial pressure (CAP) and pulse wave velocity (PWV): 3-factor model of the main effects

Indicator	**CAP**			**PWV**		
	F	**df**	**p**	**F**	**df**	**P**
Age	7.3	4	<0.001	12.0	4	<0.001
Sex	3.9	1	0.050	0.3	1	0.596
Weight alteration	8.2	4	<0.001	3.6	4	0.007
Model error		398			495	
R^2		0.200			0.134	

Table 3. Medians of arteriography indicators in the groups of children with and without fatty hepatosis

	None (n=50)	**Present (n=44)**	**p**
PWV, m/s	**5.6**	**6.5**	**0.003**
Augmentation index, %	-63.5	-63.8	0.904
Heart rate, bpm	75.0	77.0	0.927
SAP	**110.0**	**114.5**	**0.026**

DAP	57.5	60.0	0.050
Mean AP	**75.0**	**78.5**	**0.021**
Pulse AP	50.5	54.5	0.199
CAP, mm Hg	**94.2**	**101.7**	**0.014**

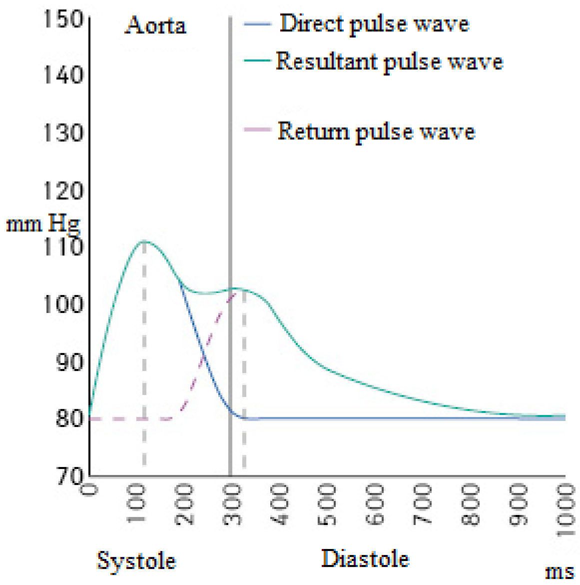
Note. Significance level (p) correlates to the Mann-Whitney test significance in the groups with and without fatty hepatosis.

Table 4. Correlation of central arterial pressure (CAP) with other arteriography indicators

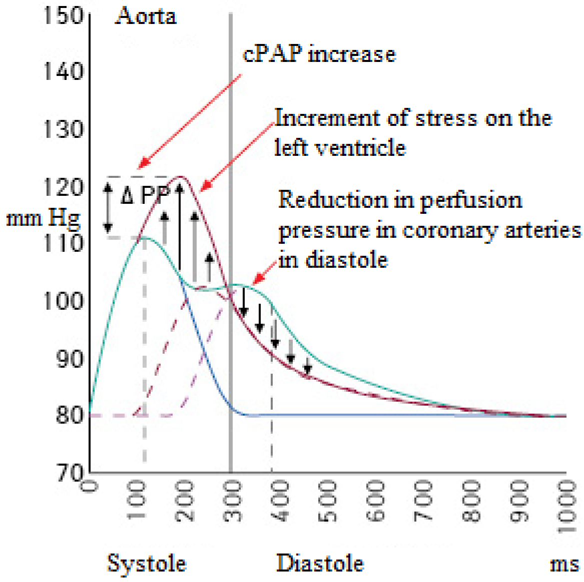
Weight alteration group	PWV, m/s	SAP	DAP	Mean AP	Pulse AP
Insufficient weight or weight deficit (n=43)	0.233	0.973	0.671	0.914	0.793
Normal weight (n=217)	0.259	0.960	0.699	0.900	0.644
Excess weight and obesity (n=148)	0.244	0.907	0.620	0.868	0.571

Note. We give coefficients of the CAP linear correlation (Pearson) with pulse wave velocity (PWV), systolic/diastolic (SAP/DAP), mean and pulse arterial pressure. All correlation are significantly different from zero, $p<0.001$, except for the CAP-PWV correlation in the group of the underweight ($p=0.132$).

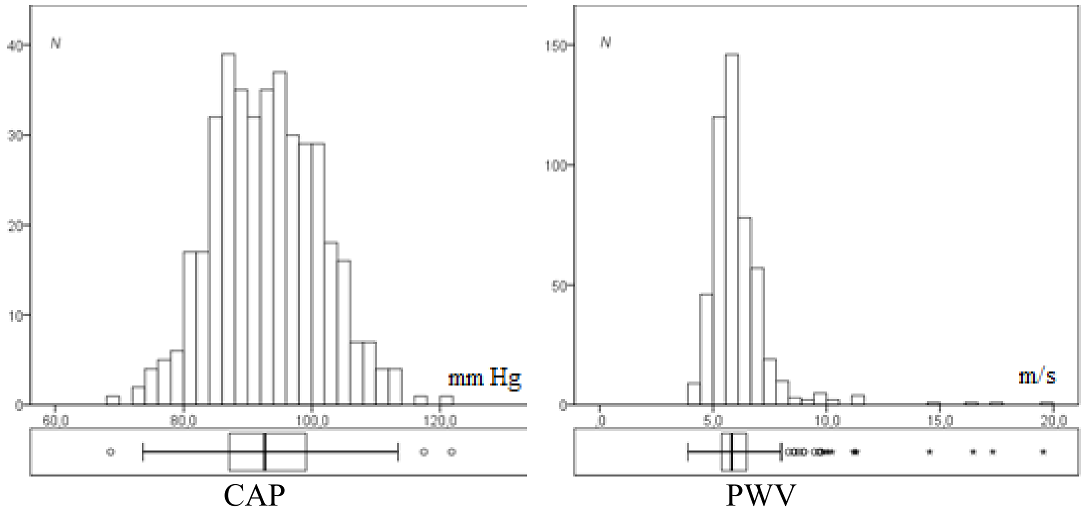
Pic. 1. Pulse wave formation [12]



Pic. 2. Alteration central (CAP) and pulse (PAP) arterial pressure in response to the early appearance of the reflected wave

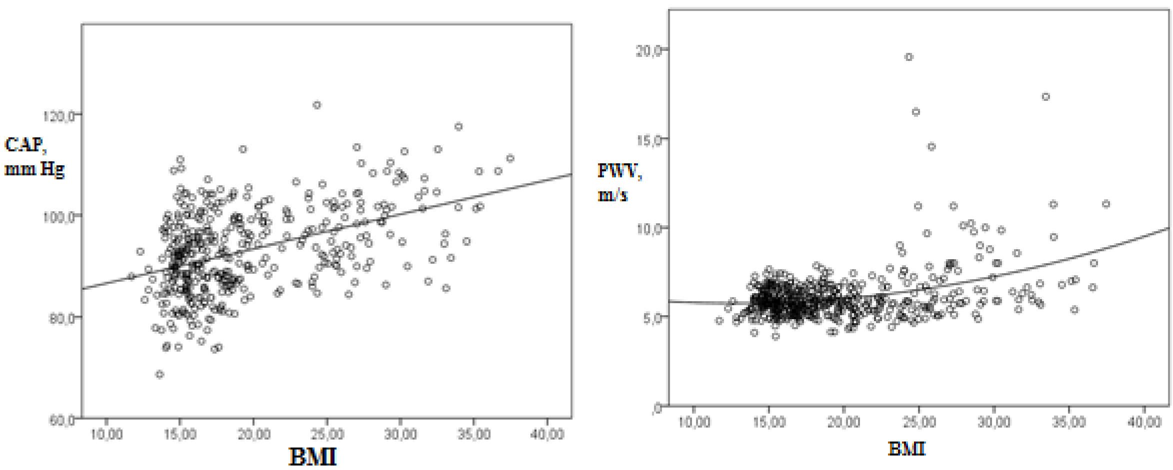


Pic. 3. Spread of central arterial pressure (CAP) and pulse wave velocity (PWV)



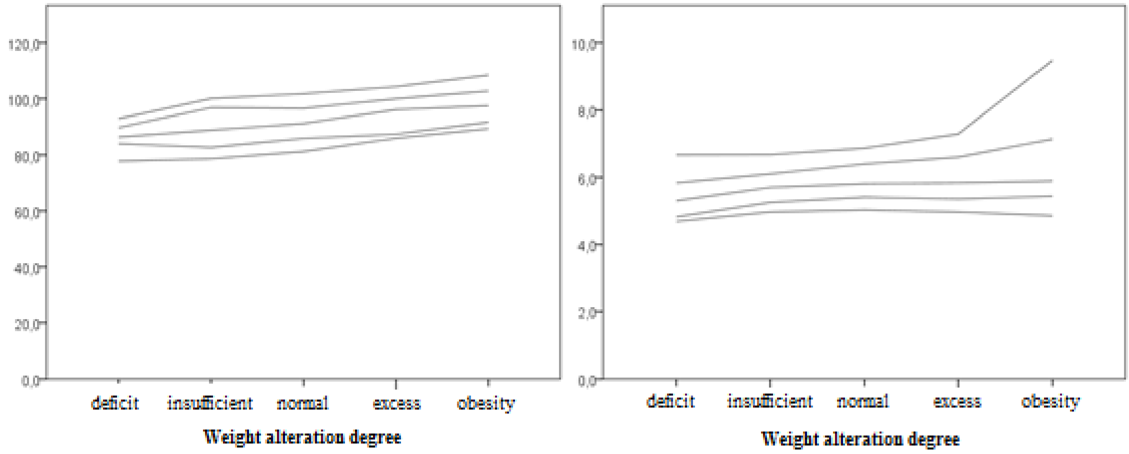
Note. A range of trials is presented in the histograms. The boxplot contains a range of the central 50% of values and 1.5 interquartile ranges (Tukey's range test); the vertical line corresponds to the median.

Pic. 4. Correlation (a) of central arterial pressure (CAP) and (b) pulse wave velocity (PWV) with body mass index (BMI)



a b

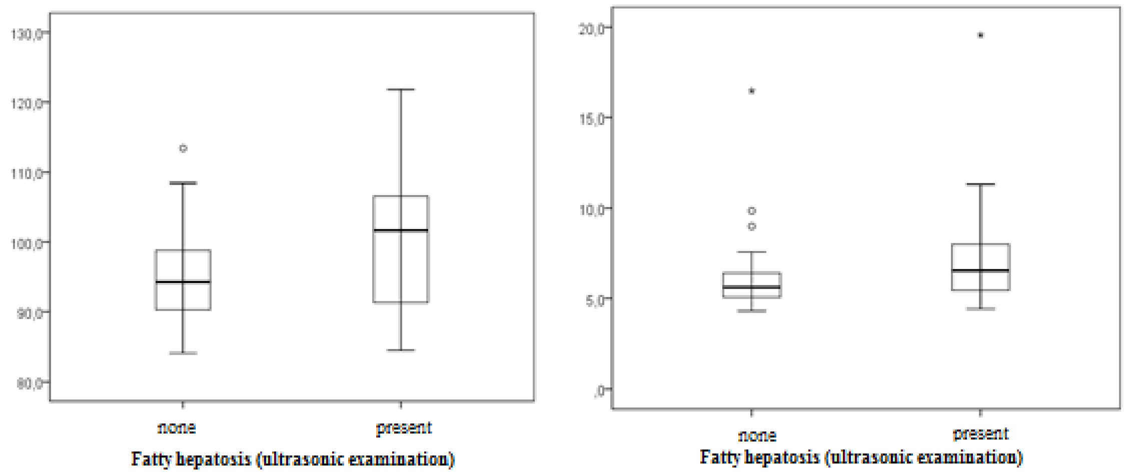
Pic. 5. Percentiles of central arterial pressure (CAP) and pulse wave velocity (PWV) in the weight alteration groups



CAP, mm Hg PWV, m/s

Note. The lines (bottom-up) represent 10, 25, 50, 75 and 90 percentiles, respectively.

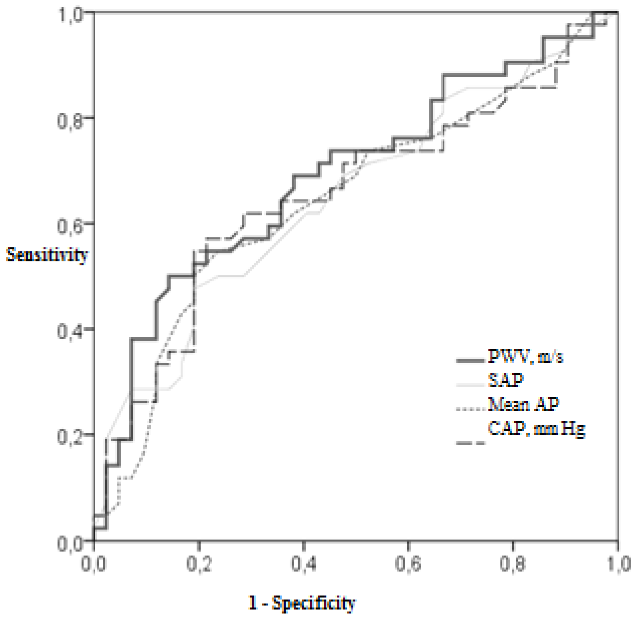
Pic. 6. Alteration of central arterial pressure (CAP) and pulse wave velocity (PWV) at fatty hepatosis



CAP, mm Hg PWV, m/s

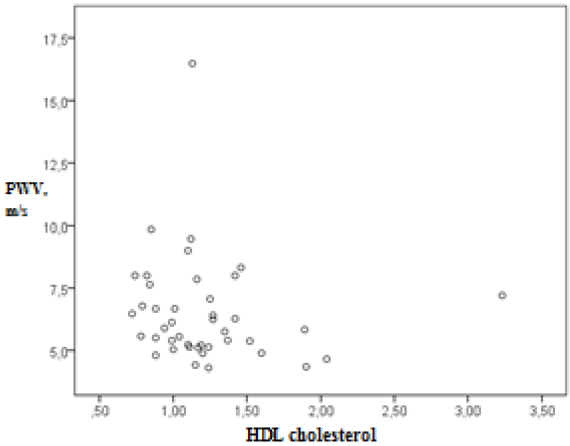
Note. The boxplot contains a range of the central 50% of values and 1.5 interquartile ranges (Tukey's range test). The horizontal line corresponds to the median.

Pic. 7. ROC-curves of specific indicators for diagnosis "Fatty hepatosis"



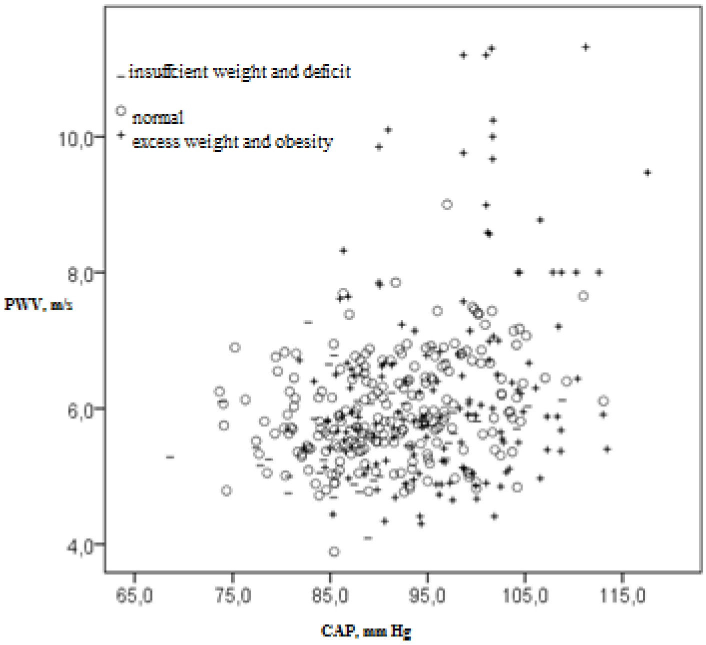
Note. PWV – pulse wave velocity, SAP/CAP – systolic/central arterial pressure.

Pic. 8. Diagram of PWV – HDL lipoprotein spread



Note. PWV – pulse wave velocity, HDL – high-density lipoproteins.

Pic. 9. Spread of patients by levels of central arterial pressure (CAP) and pulse wave velocity (PWV) in different weight alteration groups



Note. The scatter diagram does not represent several trials with PWV>12 m/s. The observation data are shifted to the right along the CAP axis.

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