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CLINICAL STUDY

Central systolic blood pressure increases with aortic stiffness

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ABSTRACT
OBJECTIVES: Central systolic blood pressure (CSBP) is the pressure in the root of aorta, which directly influences organs such as brain, heart and kidneys and is related to organ damage. Its value increases with the aortic stiffness. The aim of this study was to analyze the relationships of CSBP to aortic stiffness parameters.
METHODS: Central blood pressure (BP) and related parameters were measured by Arteriograph, working based on oscillometric principle, using pulse wave analysis (PWA) approach. We examined 123 patients (69 females, 54 males) with a primary hypertension.
RESULTS: Using a linear correlation analysis, we found that CSBP was correlated to aortic pulse wave velocity (PWV), aortic and brachial pulse pressure (PP), aortic augmentation index, return time of reflected pressure wave (RT) and aortic and brachial augmentation indexes. Multivariate analysis defines the aortic pulse pressure (PPao) as the most powerful parameter influencing CSBP. By an individual analysis of BP in each patient separately, we defined two different types of central hemodynamics; those with a higher CSBP than brachial SBP occur in stiffer aorta.
CONCLUSION: The CSBP increases with aortic PP, the most powerful stiffness parameter of aorta. Higher CSBP than brachial SBP usually accompanies a stiffer aorta *(Tab. 5, Ref. 19)*. Text in PDF *www.elis.sk.*
KEY WORDS: central systolic pressure, aortic stiffness, augmentation index.

Introduction

Central systolic blood pressure (CSBP) is the blood pressure in the root of aorta. It is the result of interaction between an ejected stroke volume from the left ventricle (which generates the primary pressure wave), the dampening function of large arteries and of propagative and reflected pressure waves in arterial tree. The value of diastolic blood pressure is considered to be the same through all arterial tree, therefore the main interest is the central systolic blood pressure and pulse pressure amplitude (PP) (1, 2, 3).

Central aorta serves as an elastic reservoir easily expanded by ejected blood from LV in systole, which prevents the steep increase of BP in systole. During diastole, previously expanded aorta passively contracts, contributing to diastolic blood pressure and flow to periphery and for coronary perfusion and prevents the steep fall of central diastolic blood pressure. Each heartbeat evokes a feedback leading to rhythmic changes of the tonus of vascular smooth muscles of arterial wall securing an optimal cooperation among left ventricle, aorta and peripheral arteries. This process is named Ventricular-vascular coupling and helps to deliver blood to periphery with the lowest possible workload of left ventricle. If the central aorta is stiff (not physiologically elastic), the left ventricular stroke volume does not expand the root of aorta during the systole appropriately, therefore the blood is ejected from LV against a higher resistance, which leads to a higher systolic pressure in aorta, and blood is forced to flow with a higher velocity away from the root of aorta to periphery. As a consequence, the primary pressure wave reaches reflection points earlier, converts to the reflected pressure wave returning with a high speed in opposite direction, reaches the central aorta and LV outflow tract very early (even before the end of the same systole, which created that primary wave) and increases systolic pressure, which must be overcome by left ventricular contraction. This is the mechanism of central blood pressure augmentation, disadvantageous for left ventricle.

The higher the stiffness, the higher is the central BP augmentation (4, 5). The standard measurement of blood pressure does not allow for the estimation of central systolic blood pressure. Several noninvasive techniques were developed for this purpose (6).

All noninvasive assessment are based on pulse wave analysis (PWA) of primary and reflected pressure waves detected by applanation tonometry on radial or carotid arteries. Newer and simpler methods are based on oscillometry, when pressure waves are sensed by the cuff fastened on arm. There are several parameters used to define the aortic stiffness. The gold standard is the carotid-

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Tab. 1. Basic characteristics of our cohort.

	All patients	Males	Females	p
Number of patients (n)	123	54	69	n/a
Age (years)	63.4±12,1	58.4±12.9	67.4±9.9	<0.001
Height (cm)	169.7±10.0	178.4±6.6	162.8±6.0	<0.001
Weight (kg)	81.7±16.3	92.2±14.1	73.4±12.7	<0.001
BMI (kg/m^2)	28.02±4.2	28.9±3.8	27.7±4.4	=0.097 (NS)
BSA (m^2)	1.9±0.2	2.1±0.2	1.8±0.2	<0.001
Brachial systolic BP (mmHg)	131.1±13.0	131.5±13.6	130.9±12.6	=0.804 (NS)
Brachial diastolic BP (mmHg)	80.6±8.4	82.3±9.4	79.3±7.5	=0.016
PP brachial (mmHg)	50.6±11.9	49.2±12.8	51.6±11.2	=0.291 (NS)
HR (pulses/minute)	67.2±9.1	68.1±9.1	66.6±9.1	=0.352 (NS)

-femoral pulse wave velocity, (cfPWV), another is the pulse pressure (PP) in aorta and brachial PP, the return time (RT) of pulse wave from periphery back to the ascending aorta. Also aortic and brachial augmentation indexes (AIx-ao, AIx-brach) are used (7).

Although the routine clinical use of CSBP measurement is under debate, a growing evidence of the prognostic significance of such an approach supports its implementation in practice in near future (8, 9).

Objective of the study

The aim of our work was to analyze the relationships between aortic stiffness and central systolic blood pressure in a group of treated hypertensive subjects and to evaluate the effect of different parameters of aortic stiffness on the level of CSBP.

Subjects and methods

In this study, we analyzed data from 123 non-selected consecutive patients (69 females, 54 males) with a primary hypertension examined in our outpatient department during the consultation or during the follow-up visits. The inclusion criteria were primary hypertension, regular sinus rhythm, stable general health condition in the time of measurement, cooperation of patient and signing of the informed consent with the participation in this study. This study was approved by the University Hospital Ethical Committee. Basic characteristics of group examined are in the Table 1.

The invasively and noninvasively validated instrument, Arteriograph Tensiomed Ltd. (H-1103 Budapest, Hungary), was used to estimate the central BP (10, 11).

It works based on the oscillometric principle, using one cuff for both BP measurement and a waveform detection for the pressure wave analysis (single-point measurement approach) (12).

The cuff for BP and central hemodynamic evaluation was tightly fastened on the dominant arm above the elbow as recommended in the user's manual (13). Arteriograph User's Manual.

The pressure waves are automatically calibrated to absolute BP value using the brachial pressure measured by Arteriograph during the same measurement cycle (13).

One measurement cycle lasts 2 to 3 minutes. Patients were examined after 5 to 10 minutes of rest in the supine position. After fasting the cuff in the proper position on the arm, each measurement was automated and operator-independent, and the results of measurements depended solely on the measuring device. Arteriograph measures central systolic blood pressure (CSBP) from pressure wave analysis and derives several parameters of central hemodynamics and arterial stiffness, such as: aortic pulse wave velocity (PWV-ao), aortic pulse pressure (PP-ao), brachial pulse pressure (PP-brach), aortic augmentation index (Aix-ao), return time of reflected pressure wave (RT).

Tab. 2. Correlation between CSBP and aortic stiffness parameters in the whole group of 123 pts.

Stiffness parameter correlated to CSBP	Mean value of stiffness parameter evaluated	Spearman correlation coefficient rs	p
Number of patients, N	123	N/A	N/A
Pulse Wave Velocity, PWV-ao (m/s)	9.3±1.6	0.253	=0.005
Aortic Pulse pressure, PP-ao (mmHg)	51.2±10.9	0.805	< 0.001
Brachial Pulse Pressure, PP-brach (mmHg)	52.17±8.9	0.632	<0.001
Aortic Augmentation index, Aix-ao (%)	32.62±11,7	0.479	<0.001
Brachial Augmentation index, Aixbrach (%)	–1.68±25.7	0.456	<0.001
Return time, RT (ms)	112.37±20.3	–0.318	<0.001

Data obtained were submitted to the standard statistical evaluation (IBM SPSS Statistics 23). For the testing of relationships between the selected parameters, we used Pearson and Spearman's correlation. Multivariate stepwise regression analysis was used for verifying a significant correlation of CSBP with stiffness parameters. The p value < 0.05 was selected as the threshold for significant differences.

Results

The whole group of 123 patients

In the whole group (men and women together), the CSBP increased with a higher velocity of aortic pulse wave, PWV-ao. Nonparametric analysis showed a significant influence of PWV-Ao on CSBP (one-dimensional analysis, Spearman correlation coefficient $r_s = 0.253$, $p = 0.005$).

Significant correlations were found also for Aortic pulse pressure (Pulse Pressure), PP-Ao) and brachial pulse pressure, PP-brach. A significant influence were found also for the value of aor-

Tab. 3. Correlation of stiffness parameters to CSBP.

Central systolic blood pressure, CSBP correlation to stiffness parameters	A Higher SBP-brach (Peripheral Amplification present) Physiological VVC, Compliant aorta		B Higher CSBP (Central Augmentation increased) Pathological VVC, Stiff aorta	
Stiffness parameter for correlation	Spearman Correlation coeff. r_s	p	Spearman Correlation coeff. r_s	p
n	60 pts (49 %)	N/A	63 pts (51 %)	N/A
Pulse Wave Velocity, PWV-ao	= 0.133	= 0.311 (NS)	= 0.271	= 0.032
Aortic Pulse pressure, PP-ao	= 0.69	<0.001	= 0.767	<0.001
Brachial PP, PP-brach	= 0.647	<0.001	= 0.843	<0.001
Aortic Augmentation index, Aix-ao	= 0.14	= 0.287 (NS)	= 0.767	<0.001
Brachial Augmentation index, Aixbrach	= 0.081	= 0.175 (NS)	= 0.473	<0.001
Return time, RT	= –0.177	= 0.175 (NS)	= –0.306	= 0.015

VVC, ventricular-Vascular Coupling
A. Correlations in the group with a higher brachial systolic pressure, SBP-brach than central one. (Physiological Ventricular-Vascular coupling; Peripheral pressure amplification present)
B. Correlations in the group with a higher central systolic pressure CSBP, than brachial one. (Non-physiological Ventricular-Vascular coupling; Central pressure augmentation increased).

Tab. 4. Comparison of stiffness parameters between the group with a higher SBP-brach against the group with a higher CSBP; (physiological Ventricular-Vascular coupling and non-physiological Ventricular-Vascular coupling.

	Higher SBP-brach (Peripheral amplification present) Physiologic VVC	Higher CSBP, (Central augmentation increased) Pathological VVC	p
Pulse Wave Velocity, PWV-ao (m/s)	9,3±1,6	9,9±1,7	=0.015
Aortic Pulse pressure, PP-ao (mmHg)	45.67±8.3	56.6±10.4	<0.001
Brachial PP, PP-brach (mmHg)	52.46±9.4	51.9±8.5	=0.719 (NS)
Aortic Augmentation index, Aix-ao (%)	23.1±7,4	41.7±6,8	<0.001
Brachial Augmentation index, Aixbrach (%)	–22.9±17,3	+18.6±12,6	<0.001
Return time, RT (ms)	119.9±19,9	105.2±18,2	<0.001

VVC, ventricular-vascular coupling

tic augmentation index, Aix-ao, and brachial augmentation index, Aix-brach and a return time (RT) of the reflected pressure wave. We could see that all stiffness parameters significantly affected the value of central systolic blood pressure. Details are in Table 2.

Peripheral amplification and central augmentation of systolic blood pressure

On the basis of the difference in the absolute values between central and peripheral systolic blood pressures, we divided the patients into two groups with strikingly different central hemodynamics.

A. Higher brachial systolic pressure (SBP-brach) than central systolic blood pressure (CSBP).

The first group with a higher brachial systolic pressure, SBP-brach than CSBP, where the peripheral amplification was obviously well present, which is a sign of a compliant aorta and physiological ventricular-vascular coupling function. This cohort consisted of 60 patients (49 % from 123 patients). The Spearman correlation coefficient for nonparametric analysis was highest for a pulse pressure in aorta, PP-ao and was highly significant ($r_s = 0.69$, $p < 0.001$) (Tab. 3).

B. The second group -higher CSBP than brachial SBP; (63 pts, 51 % from whole group)

These patients have hemodynamics with a strong central systolic augmentation, which is the sign of non-optimal ventricular-vascular coupling and stiff aorta. This type of blood pressure difference is sometimes named as missing peripheral amplification, or in another words, patients with pathologically increased central systolic augmentation, suggesting a stiff aorta.

The correlation coefficient for CSBP dependence on PP-ao was also highly significant ($r_s = 0.767$, $p < 0.001$), for details (Tab. 3).

We can see, that in patients with compliant aorta, only aortic and brachial PP significantly correlated with CSBP. In patients with stiff aorta, all evaluated parameters significantly correlated with CSBP.

In Table 4 we can see the changes of the mean values of stiffness parameters after splitting the entire cohort into two subgroups according to a higher CSBP or a higher brachial SBP.

Multivariate analysis

To test the impact of parameters on CSBP values, a multidimensional linear regression model was used. The reverse method for parameters selection was applied. The analysis started from the full model with all possible explanatory variables. Based on the multivariate statistical methods, a significance of each parameter (regression coefficient) defined in the tested model was estimated. Subsequently, a parameter with the highest p-value greater than the given significance level ($p = 0.1$) was dropped from the model. In the second step, a submodel with all other parameters except of the one excluded in previous step, was tested in the same way as before. The procedure was repeated until only statistically significant parameters remained.

Tab. 5. Multivariate analysis. Correlation of Central Systolic BP with stiffness parameters.

Multivariate analysis- Correlation of CSBP with stiffness parameters	n	Most significant stiffness parameter	Correlation coefficient ß	p
All patients	123	Pulse Pressure in Aorta, PP-ao	β = 0.987	=0.0007
Higher Brachial SBP Physiological Ventricular-Vascular Coupling (Peripheral SBP amplification present)	60	Pulse Pressure in Aorta, PP-ao	β = 0.224	= 0.044
Higher Central SBP Pathological Ventricular-Vascular Coupling (Central SBP augmentation increased)	63	Pulse Pressure in Aorta, PP-ao	β = 1.723	<0.001

Using a multidimensional linear regression model, we found that aortic pulse pressure, PP-Ao, had the strongest influence on CSBP in the whole group of 123 pts. The regression coefficient (beta) β = 0.987, p = 0.007. Other parameters were indicated as nonsignificant.

Moreover, using a multidimensional linear regression model on the subgroup of 60 patients with a higher brachial systolic blood pressure, SBP-brach than the central one, we revealed that the strongest effect on CSBP had the aortic pulse pressure, PP-ao. The regression coefficient (beta) β = 0.224, p = 0.044. Other parameters were indicated as nonsignificant. Likewise in the 63 pts set, with a higher central systolic blood pressure, CSBP, than the brachial one, we found that the strongest effect on CSBP had PP-Ao. The regression coefficient (beta) β = 1.723, p < 0.001. Other parameters were indicated as nonsignificant (Tab. 5).

Resulting from the multivariate analysis, PP-ao showed to be as the strongest parameter affecting CSBP in whole group as well as in both subgroups A and B.

Discussion

The interest of clinicians to central hemodynamics increased after the results of CAFE study in 2006 were released, where authors explained the difference in cardiovascular outcome of treated hypertensive patients by a difference in the achieved central systolic blood pressure (7, 15).

The relationships between the brachial and central systolic pressure are very complex and are subjects to many influences (16). The cohort of our patients was non-homogenous (details in Table 1) what might influence the results, but our aim was to concentrate on the resulting central systolic blood pressure and aortic stiffness parameters as a part of patients characteristics. Aortic stiffness is very substantial and powerful parameter influencing blood pressure and central hemodynamics as reported in many papers (6, 12, 14). The aim of our work was to compare several stiffness parameters with different strength or influence on central hemodynamics. The Aortic Pulse Wave velocity (PWV) is considered the gold standard for a definition of stiffness (3, 6). Its influence on CSBP in our group of patients was found as relatively high, with the correlation coefficient (r = 0.253) and a high level of significance (p = 0.005).

Aortic and brachial PP are closely bound to brachial and central pressures and to target organ damage (17), therefore we supposed a tight correlation of pulse pressure to CSBP.

Firstly, we evaluated the whole group together, all 123 patients, and found a significant correlation of each single stiffness parameter to central pressure. Details in Table 2.

When we evaluated the central and brachial pressures individually, in each patient separately we found that whole group was splitting into two patterns. First subgroup had the central blood pressure lower then the brachial one, which was in agreement with the prevailing opinion in literature. The proportion of these patients was 49 % from 123 persons.

The second subgroup, 51 % from 123 persons, had their central systolic BP higher than the brachial one. This finding is in discrepancy with the prevailing opinion, that brachial blood pressure should be higher because of peripheral amplification by summation of primary and secondary pressure waves meeting on the periphery (14). After the analysis of these two cohorts, we found different central hemodynamics characteristics, namely in the parameters of stiffness.

The subgroup with a higher brachial systolic pressure then the central one (with physiological ventricular-vascular coupling and elastic aorta), retained s significant correlation of stiffness to CSBP only for central and brachial PP after statistical evaluation (Tab. 3A).

The second subgroup had a higher central than brachial SBP (it means the patients had stiff aorta and non-physiological ventricular-vascular coupling function). This finding was in contrast to current opinion presented in literature (14). The proportion of patients with a higher central than brachial BP in our cohort was 51 % of 123 patients. In this subgroup, after a statistical reevaluation, all stiffness parameters remained to correlate significantly with CSBP, not only brachial PP and aortic PP (Tab. 3B). This type of results, when CSBP is higher than Brach-SBP, is practically not presented in literature. The reason may be fact that patients are evaluated only as the whole cohort and important individual details remain hiden in global mean values.

In Table 4, we can see changes in the mean values of stiffness parameters after splitting the entire cohort into subgroups. It is notable, how the original values from the whole cohort (for comparison see Table 2) were subdivided into two columns, with an increasing extrema for stiffness in the subgroup with stiffer aorta.

Brazilian authors (18) in the set of 260 patients had measured systolic pressure in the aorta during catheterization. All patients over 50 years of age (208 patients), had a higher central systolic pressure than the brachial systolic pressure, which was measured oscillometrically. Blood pressure amplitude (PP) was also higher than on brachial artery. Such publication with a finding of higher

central than peripheral systolic pressure is unique and supports our results.

Anglo-Cardiff Collaborative Trial II presented data that in a large proportion of patients, the BP values of central and peripheral BP overlapped in the range between high normal and hypertensive stage I, from which we may suppose that a part of cohort had a higher central pressure than peripheral blood pressure (19). With multivariate analysis we found that most powerful stiffness parameter which correlated to central systolic blood pressure was the amplitude of aortic PP (ß = 1.723, $p < 0.001$); it was for the subgroup with higher CSBP, but this parameter was highly significant for all three cohorts (Tab. 5).

In current literature, we can find many papers strongly recommending measuring CSBP because it brings more complex view to central hemodynamics and enables more exact evaluation of effectiveness of antihypertensive therapy (2, 17).

Learning points

- Central Systolic Blood Pressure directly influences target organs such as heart, brain and kidneys.
- Many studies indicate that Central systolic blood pressure is more strongly related to organ damage and future cardiovascular events than the brachial blood pressure.
- Antihypertensive drugs may have different effects on the central and brachial blood pressures.
- Noninvasive modern devices may provide a more accurate diagnosis and may improve the control of hypertension treatment (approaching closer to personalized medicine).

Conclusions

In our group of treated hypertensive patients, we found that the most important stiffness parameter which correlated with central systolic blood pressure was the amplitude of aortic pulse pressure (PP-ao).

A significant influence we found also for the brachial pulse pressure (PP-brach), return time of reflected pressure wave (RT), aortic pulse wave velocity (PWVao), aortic augmentation index (Aix-ao) and brachial augmentation index (Aix-brach).

From the whole cohort of 123 evaluated patients, 51% had a higher central systolic blood pressure than the brachial systolic blood pressure.

This finding is in contrary to prevailing opinion that central systolic blood pressure should be lower than brachial systolic blood pressure because of the peripheral amplification by a reflected pressure waves.

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