International Heart
and Vascular Disease Journal • Volume 2, Number 3, June 2014
Journal of the Cardioprogress Foundation

Aortic stiffness and the possibility of its drug correction in patients with hypertension and obesity

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Abstract
Numerous studies confirm the importance of assessing aortic stiffness in determining the risk of cardiovascular events in patients with hypertension and obesity, and the need for medications for its medical correction. Most of the antihypertensive drugs have, in varying degrees, a direct or indirect effect on arterial stiffness. That is why the use of combination therapy may be more effective. Lipid-lowering and antidiabetic therapy has an additional effect on vessel stiffness in these patients. However, data on the effect of diet and weight-reducing drugs on the condition of large vessels are few and require clarification.

Keywords
Hypertension, obesity, aortic stiffness, central blood pressure, pulse wave velocity

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Numerous epidemiological and clinical studies have shown that aortic stiffness is an important factor in evaluating the prognosis of cardiovascular disease in patients with hypertension and obesity. According to studies, pulse wave velocity (PWV), central pressure, as well as parameters of the reflected waves are independent predictors of cardiovascular (CV) events in different groups of patients. An interesting study, conducted by Guerin *et al.*, involved 150 patients, aged 52 ± 16 years, with severe chronic kidney disease (CKD). All patients had two measurements of their carotid-femoral PWV and were prescribed antihypertensive therapy with angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs) and / or beta-blockers. During follow-up (51±38 months), 59 patients died, 40 of them from cardiovascular disease (CVD). Analysis of the results showed that, despite comparable BP reduction, in the group of deceased patients there was an increase in PWV. Thus, the value of PWV was an independent death risk factor from CVD [1].

The CAFE (Conduit Artery Function Evaluation) study included 2,199 patients aged 40–79 years with hypertension and at least three additional risk factors for CV events (smoking, hypercholesterolemia, microalbuminuria, diabetes, etc.). Mean body mass index (BMI) of participants was 29±4.6 kg/m². During follow-up (average 4.5 years), all patients had central pulse wave analysed, and PWV was determined. To identify predictors of CV events, several variants of multifactorial regression analysis were performed: PWV, central BP, and the characteristics of the reflected waves were assessed separately or in conjunction with age and main risk factors, the data of all enrolled patients or patients without a history of CVD were analysed. In all models, central pulse pressure, as well as peripheral, proved to be a significant predictor of CV events in this category of patients. Increase of central pulse pressure by 10 mmHg raises the risk of CV events, on average, by 1.2 times [2].

Data from the CAFE study were confirmed in the Strong Heart Study, involving 3,520 participants. Mean age was 58±14 years; mean BMI — 31.5±6.8 kg/m². According to multifactorial regression analysis, central pulse pressure was an independent predictor of CV events and was exceeded by the significance of peripheral pulse pressure in individuals older than 62 years. It was also noted that an increase in central pulse pressure by more than 50 mmHg was associated with a high risk of CV events, regardless of a participant's sex and age [3].

In a study conducted by Wang, data from 1,272 patients aged 30–79 years were analysed. During follow-up (10.8±1.7 years), 130 people died, including 37 from CVD. According to multifactorial regression analysis, central systolic BP was the most significant predictor of aortic stiffness. The increase in central systolic BP by 10 mmHg raised the risk of CV events by 1.3 times [4].

Data on the prognostic significance of the reflected wave parameters are contradictory. In some studies, involving small groups of patients, it has been shwon that augmentation index (AIx) is an independent predictor of CV events, not yielding, and according to some data, even exceeding the prognostic value of central pulse pressure [5–6]. However, in large multicenter trials these data were not confirmed.

Thus, most researchers point out the importance of assessing aortic stiffness in determining the risk of CV events, and the need for medications for its medical correction. Pharmacological agents capable of reducing arterial stiffness include antihypertensive, lipid-lowering, antidiabetic, and also weight loss medications. The drug effect on aortic stiffness can be direct, caused by direct influence of a drug on the arterial wall, and indirect, associated with a decrease in BP, peripheral vasodilatation, changing in the parameters of the reflected wave, and a decrease in heart rate. It is assumed that the most pronounced direct effect on aortic stiffness is from ACE inhibitors and angiotensin receptor blockers (ARBs), and, to a lesser degree, CCBs and aldosterone antagonists. Drugs that have an indirect effect include CCBs, diuretics and, to a lesser extent, ACE inhibitors and ARBs. Currently, special attention is paid to the influence of ACE inhibitors and ARBs on the remodeling of the aortic wall. Studies show that long-term administration of drugs in this group is accompanied by an improvement of elastic properties in large arteries, regardless of the hypotensive effect. In a study, conducted by Tropeano *et al.* (Diabetes Artery Perindopril Hypertension Normalization Excess sTiffness — DAPHNET), 57 patients with hypertension and type II diabetes aged 56–70 years were recruited. Within 6 months after the normalization of the peripheral BP, patients received 4 or 8 mg dose of perindopril. All patients underwent applanation tonometry, ultrasound of the carotid arteries. During the therapy, both groups showed a decrease of central BP, improvement in the elastic properties of the carotid artery and, in particular, reduction of intima-media thickness, which was more pronounced in patients treated with 8 mg of perindopril. Thus, a direct dose-dependent effect of the drug on the stiffness of large arteries was demonstrated [7].

In a study, conducted by Mackenzie, 59 patients were involved with isolated systolic hypertension aged 62–74 years. Patients were taking perindopril over 10 weeks. All patients underwent applanation tonometry, and PWV was determined. In the background of a significant reduction in peripheral and central BP, no changes in PWV were identified. The study authors suggest that the lack of dynamics in carotid-femoral PWV is associated with a short period of treatment [8].

Tomiyama *et al*. conducted a study involving 134 patients with stage I–II hypertension. All patients were treated with candesartan for 2–3 years. In the background of prolonged use of the drug there was a significant decrease in PWV, on average by 2.0±0.18 m/s [9].

There are not many studies evaluating the effect of aldosterone antagonists on aortic stiffness. Thus, Kithas & Supiano describe the results of their study, which involved 45 hypertensive patients from a relatively older age group (mean age 69 years). All patients underwent ambulatory blood pressure monitoring (ABPM), applanation tonometry, and PWV was measured. During 6-month therapy of spironolactone there was a significant decrease of PWV, an average of 1 m/s. The authors suggest that the decrease in PWV was due to the suppression of the arterial wall remodeling processes activated by aldosterone, and to an increase in the aorta elasticity [10].

Among the drugs that have indirect (mediated) effects on aortic stiffness, a special place is occupied by CCBs. Due to peripheral vasodilation, drugs in this group increase the propagation time of the reflected wave from the reflection points to the ascending aorta, reduce the amplitude of the reflected wave, and ultimately, reduce central systolic and pulse pressure. In a study, conducted by Palombo C., Malshi E., Morizzo C., 41 patients, aged 50–64 years, with stage I–II hypertension were involved. During the observation period (6 months), all patients underwent ultrasound examination of the carotid arteries, analyses of central pulse wave and local arterial stiffness. In the background of the therapy with long-acting CCB there was found a significant decrease in peripheral and central BP and AIx by reducing the amplitude of the reflected wave. At the same time the indicators of local stiffness of the carotid artery did not change [11]. Several other studies have shown that when compared with ACE inhibitors or ARBs, CCBs have a less pronounced effect on PWV, whereas peripheral and central BP reduces in all groups equally [9].

Data on the effect of thiazide diuretics on aortic stiffness are limited and conflicting. Most of the studies comparing the efficacy of antihypertensive drugs of different classes, mentioned lack of influence of diuretics on central BP, parameters of the reflected wave, and PWV. However, in a trial, conducted by Dart *et al.* (ANB2-Second Australian National Blood Pressure Trial), it was shown that prolonged use of hydrochlorothiazide in 199 hypertensive patients aged 65–84 years was accompanied by a significant reduction in central BP, comparable with the effect of ACE inhibitor — enalapril [12].

Recently, particular attention has been paid to the effectiveness of combination therapy, consisting of antihypertensive drugs of different classes.

Asmar *et al*. (REASON — Preterax in regression of Arterial Stiffness in a controlled double-blind study) evaluated the effect of combination in low doses of perindopril and indapamide on peripheral and central BP, parameters of the reflected wave and PWV in comparison with atenolol. The study included 354 patients with hypertension aged 18–84 years. During the observation period (12 months), all patients received applanation tonometry, central pulse wave analysis, and PWV was determined. In the background of the combined therapy, statistically significant reduction was shown in central systolic and pulse pressure, AIx, and PWV. In the atenolol group, there was a significant decrease of PWV, more pronounced than in the perindopril / indapamide group, however, central BP changed insignificantly, with the AIx slightly increased. The study authors suggest that the positive effect of perindopril / indapamide on central BP and PWV was due to a combination of direct and indirect effects of drugs on aortic stiffness. Insignificant effect of atenolol on central BP and parameters of the reflected waves, according to the authors, was due to the slowing of the heart rate, lengthening the period of exile and, as a consequence, an increase in central systolic and pulse pressure [13].

Williams *et al*. (CAFE) evaluated the effect of amlodipine and perindopril combination on peripheral and central PB, parameters of the reflected wave and PWV in patients with hypertension, compared with atenolol and thiazide diuretic combination. In the background of the prolonged combination therapy there was a significant decrease in peripheral BP in both groups. In the amlodipine / perindopril group there was revealed a more pronounced reduction of the central BP, as well as reflected wave characteristics such as pressure augmentation and AIx. Carotid-femoral PWV in both groups decreased slightly, on average by 0.5 m/s. According to the authors, the lack of central BP reduction in the atenolol group is not

only due to slowing of the heart rate, but also to peripheral vasoconstriction, which led to shortening of the distance from the reflection points to the ascending aorta, increase in the amplitude of the reflected wave, and central systolic blood pressure [2].

Similar results were obtained in a study, conducted by Boutouyrier *et al*. (EXPLOR), which involved 393 patients with hypertension aged 47–67 years. In the background of the combined amlodipine / valsartan therapy for 6 months, a significant reduction of central BP and AIx was shown, whereas in the amlodipine / atenolol group the central systolic BP decreased slightly, and the AIx increased. PWV significantly decreased in both groups, on average by 0.97 m/s. The study authors suggest that this atenolol effect is associated not only with the heart rate and the influence on peripheral vessels, but also with the lack of direct effect of the drug on aortic stiffness, in contrast to the combination of an ACE inhibitor and CCB [14].

Many authors believe that the main reason for the lack of beta-blockers influence on central BP is a decrease in heart rate, but according to some studies, a significant decrease in heart rate caused by drugs of other classes is not always accompanied by increase in AIx and central systolic BP. Topouchian *et al*. evaluated the effect of verapamil, trandolapril and their combination on the large arteries stiffness in 69 patients with hypertension aged 29 to 76 years. During the 7 month follow-up, all patients in the dynamics were carried out applanation tonometry, ultrasound of the carotid arteries, and carotid-femoral PWV was determined. Despite the decrease in heart rate, in all groups there was revealed a significant decrease in central systolic and pulse pressure, PWV (an average of 2 m/s), as well as improvement of the carotid artery elastic properties, which was more pronounced in the background of the combined therapy [15].

In a study, conducted by Matzui *et al*. (Japan-Combined Treatment with Olmesartan and a Calcium Channel Blocker Versus Olmesartan and Diuretics Randomized Efficacy — J-CORE) there was compared the effect of long-acting CCB and thiazide diuretic in combination with ARB on central BP and PWV in 207 hypertensive patients. Selected by researchers CCB had a negative chronotropic action due to suppression of the sympathetic nervous system activity. In the background of the combined CCB and ARB therapy for 6 months it was showed a significant reduction in central systolic and pulse pressure, AIx and PWV. The combination of ARB and thiazide diuretic was less effective. According to the authors, the reduction of the central BP, to a greater extent, depended not on heart rate, but on peripheral vasodilation [16].

Recently there have been several comparative studies of beta-blockers, with special attention given to the medicine with vasodilating properties. Mahmud *et al*. evaluated the effect of nebivolol and atenolol on central BP, parameters of the reflected wave and PWV in 40 hypertensive patients aged 48–50 years. In both groups there was a significant decrease in peripheral BP and heart rate, but only in the nebivolol group there was a reduction in AIx, which led to a significant reduction in central pulse pressure. PWV decreased in both groups equally, on average by 2 m/s [17].

Similar results were obtained by Shah *et al*. (Carvedilol Reduces Aortic Wave Reflection and Improves Left Ventricular / Vascular Coupling: A Comparison with Atenolol — CENTRAL), where 41 patients with stage I–II hypertension were involved. The study assessed effect of carvedilol and atenolol on central BP and reflected wave parameters. Despite a comparable decrease in peripheral BP and heart rate, in the carvedilol group a significant decrease in AIx and augmentation pressure was revealed, whereas in the background of receiving atenolol these indices increased [18].

Thus, numerous studies suggest that antihypertensive drugs of various classes have different effects on aortic stiffness characteristics such as central BP and PWV.

Recently, there have been studies on the effect of lipid-lowering and anti-diabetic drugs on aortic stiffness. It is assumed that combined antihypertensive and metabolic therapy leads to a more pronounced positive impact on arterial stiffness in patients with hypertension and obesity through previously unexplored mechanisms.

Manisty *et al*. analyzed data from 283 patients with hypertension who participated in the substudy ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial — Lipid Lowering Arm). 142 patients were receiving, in addition to combined antihypertensive therapy, atorvastatin in a daily dose of 10 mg for 6 months, 141 patients received placebo. All patients underwent applanation tonometry with the central pulse wave analysis. In the background of the atorvastatin therapy there was revealed a significant decrease in carotid AIx, compared with placebo. Substantial, but insignificant decrease was noted in the central systolic BP in patients taking a combination of amlodipine/perindopril and atorvastatin. Positive effect of atorvastatin on the reflected wave parameters, according to the

authors, is due to the drug impact on the endothelium and release of NO, as well as its anti-inflammatory properties [19].

The CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) study involved 462 patients with type II diabetes, and normal and high BP. The average age of the participants was 60±8.1 years, mean BMI — 32±5.1 kg/m². All patients had ultrasound of the carotid arteries at baseline, after 24, 48 and 72 weeks of hypoglycemic therapy. In the background of the prolonged pioglitazone therapy there was shown an improvement in elastic properties of the carotid arteries, particularly a small decrease in intima-media thickness. The study authors suggest that the positive effect of the drug on arterial stiffness is associated not only with its main, but also with its additional anti-atherogenic and anti-inflammatory effect [20].

Data on the effect of diet and drugs that reduce weight on arterial stiffness are few. For example, in the SAVE study (Slow the Adverse Effects of Vascular Aging) there were included 339 patients with abdominal obesity between ages 20 to 45 years and BMI of 25 to 39.9 kg/m². All patients at baseline and after 6 months of non-pharmacological correction (diet) had carotid-femoral PWV determined. With the reduction in weight there was observed a significant decrease in PWV, accompanied by normalization of carbohydrate metabolism that, according to the authors, was due to the reduction of quantity of metabolically active adipose tissue, reduction in sympathetic influence on the blood vessels, and decrease in heart rate [21].

Similar results were obtained by Cooper *et al.*, where 344 patients with overweight and obesity between ages 20 to 45 years were involved. With the reduction in weight during 12 months there was a significant decrease in PWV. According to the authors, mechanisms of the effect of obesity on aortic stiffness require further study, and may be linked to the influence of pro-inflammatory cytokines produced by excess adipose tissue [22].

Thus, currently there are two main variants of the impact on the large arteries stiffness in patients with hypertension and obesity: direct (independent of BP level) and indirect (associated with BP, heart rate, condition of peripheral vessels). Long-term use of ACE inhibitors and ARBs is accompanied by improvement in the aorta elasticity. CCBs and diuretics have the most pronounced indirect effect on arterial stiffness due to peripheral vasodilatation. Most antihypertensive drugs have direct and indirect effects on blood vessels in different degrees; however, combination therapy may be more effective. Beta-blockers, among other drugs, significantly reduce the pulse wave velocity. Certain drugs of this class, such as atenolol, have little effect on the pressure in the aorta. Beta-blockers, which have vasodilating properties, significantly reduce central BP. Lipid-lowering and anti-diabetic drugs have additional influence on aortic stiffness due to metabolic and anti-inflammatory effect. Data on effect of non-pharmacological correction of obesity on the state of the aorta are few and require clarification.

Conflict of interest: None declared

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