

THE INFLUENCE OF ANGIOTENSIN CONVERSION ENZYME INHIBITORS (ACEI) AND OF ANGIOTENSIN II RECEPTOR ANTAGONISTS (ARA) OVER THE AORTIC STIFFENING INDICES (PWVA₀, AIx_{A0}) IN ARTERIAL HYPERTENSION OF THE ELDERLY

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Keywords: PWV, AIx, aortic stiffening, ACEI, ARA, hypertension in elderly

Abstract: Clinical research data proved that isolated systolic arterial hypertension situations or those with high pulse pressure (PP), found more frequently in the older patients, are characterized by a process of stiffening of the large vessels, due to a degradation of the elastic tissue found in the medium tunica, which is then replaced by collagen fibres.(1,2) From a haemodynamic point of view, the stiffening of the Aorta leads to an increase of the Pulse Wave Velocity (PWV) and to an increase of the Augmentation Index (AIx) at the central level.(3,4) The new guides of the Arterial Hypertension European Society concerning the management of hypertension allotted separate subchapters to the central arterial hypertension, the vascular complications of arterial hypertension, and especially to the stiffening of the large vessels. The evaluation of the hypertensive patient should include PWV, wherever possible.(5)

Cuvinte cheie: PWV, AIx, rigidizare aortică, ACEI, ARA, hipertensiune vârstnic

Rezumat: Date de cercetare clinică au evidențiat că formele de hipertensiune arterială sistolică izolată sau cele având presiunea pulsului (PP) crescute, întâlnite mai frecvent la pacientul vârstnic, sunt caracterizate de un proces de rigidizare a vaselor mari, datorită degradării țesutului elastic din tunica medie, înlocuit de fibre de collagen.(1,2) Din punct de vedere hemodinamic, rigidizarea aortei duce la creșterea vitezei unde de puls (PWV) și la creșterea indicelui de augmentare (AIx) la nivel central.(3,4) Noile ghiduri ale Societății Europene de Hipertensiune Arterială, referitoare la managementul hipertensiunii au alocat subcapitole separate presiunii arteriale centrale, complicațiilor vasculare ale hipertensiunii arteriale, în mod special rigidizării vaselor mari. Din evaluarea pacientului hipertensiv ar trebui să facă parte și PWV, atunci când acest lucru este posibil.(5)

The vascular stiffness comes before atherosclerosis, as a supplementary risk factor to those already known so far.(6)

The evaluation of the vascular stiffness is not indicated only in clinical cases, but for asymptomatic patients as well.

The European Society for Hypertension (ESH) presented the new guidelines at the annual Congress at Milan in June 2007 (Guideline in the treatment of arterial hypertension), with the modifications concerning the diagnosis and the risk factors. As a novelty, they included the increase of arterial stiffness in the score used to include patients as being at high/very high risk of developing cardiovascular disease.

The high stiffness of the arterial wall, respectively the high propagation velocity of the pulse wave itself, situates the patient in a group of high/very high risk.(5) The aortic stiffness has a predictive value irrespective of the mortality of any cause or of the cardiovascular mortality, of fatal and non-fatal coronary events, and of fatal stroke events in essential arterial hypertension (7-9), in Diabetes mellitus (10), for patients with terminal chronic renal impairment (11,12), for elderly patients (13,14) and for the general population.(15-17)

This observation indicates that the aortic stiffness has a better predictive value than any other classic risk factor itself.(18) Following these observations, the aortic stiffness became an indicator of the large vessels state of health, with the

recommendation of inclusion in the evaluation of hypertensive patients.(5)

The role of the aortic stiffness in the increase of cardiovascular risk is explained by a series of mechanisms that determine left ventricular hypertrophy, aggravation of myocardial ischemia, the incidence of stroke. Isolated systolic hypertension, induced by the stiffening of the Aorta, represents an increased afterload, for the left ventricle, that triggers a secondary manifestation of a concentric remodeling.(19) The increase of the mass of the left ventricle represents itself a negative prognostic factor. The progression of the arterial stiffness in the large vessels can increase the risk for stroke due to the increase of the central PP, vascular remodelling with the probability of rupturing of the buildup plaque (aa. carotidae and Aorta) and the extension of the lesions in the white substance.(20)

PWV does not represent the velocity of blood flux, but the velocity of propagation of the pressure wave, and it is mainly influenced by the elasticity of the aortic wall.

Each heartbeat generates a pulse wave which is propagated from the heart in the direction of the sanguine flow. The more rigid the arterial wall, the more the pulse wave's velocity is increased. When the pulse wave reaches an arterial bifurcation, it is reflected backwards, to the origin point. Normally, the reflected wave reaches the origin point after the closing of the aortic valves, amplifying the diastolic pressure

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and the blood flow in the coronary arteries. When PWV increases and the velocity of the reflected wave increases consequently, the PWV reaches the origin point before the aortic valves close, leading to an increase of the systolic blood pressure and decreasing the contribution of the reflected wave in the coronary blood flow. This phenomenon can be quantified through the augmentation index (AIxAo), defined as the difference between the second and the first systolic peak (P2-P1), expressed as percentage of the pulsed pressure.

These two parameters can be measured by a device named arteriograph.

The measurement with an arteriograph implies the usage of a handcuff that is applied on the arm. The device inflates the cuff at a pressure that oversteps the systolic pressure by at least 35 mmHg, realizing the occlusion of the brachial artery (stop flow condition) and in these conditions the superior margin of the inflated cuff behaves as a membrane (diaphragm) overlapping the brachial artery. The variations of the central pressure, the systolic precocious wave (direct P1), the tardy one (reflected P2), as well as the diastolic wave, reaching the occlusion, act upon the membrane (diaphragm) and can be measured.

Figure no. 1. The principle of measurement – stop-flow condition

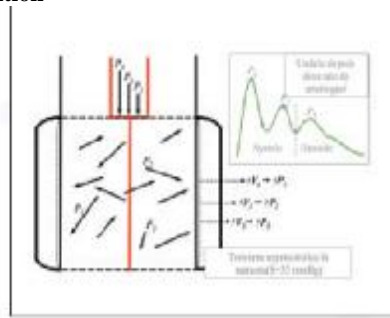


Figura 18. Principiul măsurării - stop-flow condition

In the above figure, we can notice the pressure-curve measured by the arteriograph under an oversystolic pressure. There can be noticed the systolic precocious wave (P1), the tardy wave (P2), the moment the aortic valve closes and the diastolic wave (P3). The signals are transmitted by the tonometer at a computer through a wireless system. The processing of data is made by software.

Figure no. 2. Measuring the propagation of the pulse wave velocity

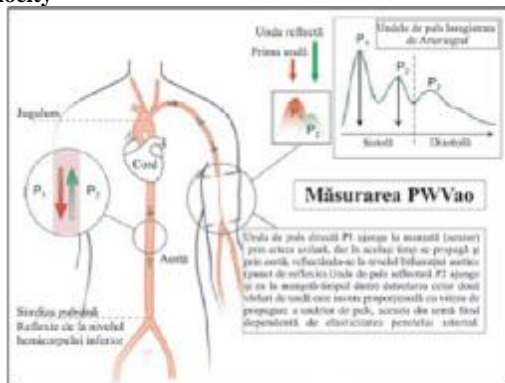
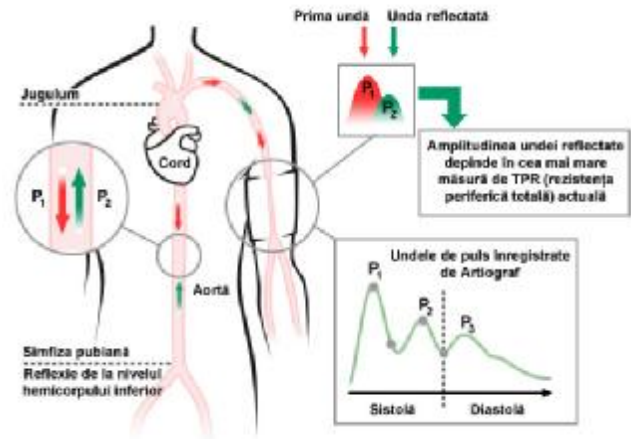


Figura 8. Măsurarea vitezei de propagare a undei de puls

The decrease of the Aorta elasticity leads to an increase in PWVAo. PWVAo is an independent predictor of the

cardiovascular mortality.(21) The pulse wave velocity is recognized as being the gold standard in determining the level of arterial stiffness.(6) The Augmentation Index of the Aorta is used as a surrogate of the Aortic stiffness. The value of AIxAo depends on the arterial elasticity and on the peripheral vessel resistance (small arteries and arterioles). The smaller the peripheral vessel resistance, the smaller Aix will be, and vice versa. When the peripheral resistance increases (endothelial dysfunction), the reflected pressure is higher ($P_2 > P_1$). It represents the measure of the real dilatation capacity of the arterioles and provides information concerning it. High values of the Aix measured with the arteriograph are strongly correlated with the altering of the dependent endothelial vasodilatation. Aix is an indicator of the endothelial dysfunction which can be ameliorated through medication, proved by the CAFE study.(22) The augmentation index has, irrespective of the classic cardiovascular risk factors, a prognostic value, and it can predict cardiovascular events even in the absence of these.(23,24)

Figure no. 3. Measuring the amplitude of the reflected wave



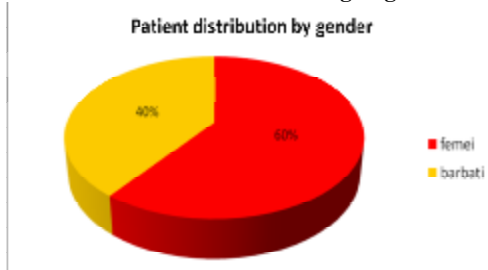
The augmentation index measurement

The vascular stiffness is augmented by the arterial hypertension. We noticed an increase of the vascular stiffness in the elderly, due to the fibrosis phenomenon. In elderly patients, the increase of blood pressure is in strict dependency of the aortic fibrosis and stiffness. Arterial hypertension causes changes in the vascular geometry, with proliferation of fibroblasts, altering of the collagen netting and the increase of the perivascular interstitial collagen, promoted by the renin-angiotensin-aldosterone system.(25,26) ACEI and ARA are two pharmacological classes of medicines which, by antagonizing the effects of the renin-angiotensin-aldosterone system, reduce the depositing of interstitial collagen and fibrosis (27,28), ameliorate the aortic distensibility (29), ameliorate the endothelial dysfunction, reduce the arterial pressure and, thus, the peripheral vascular resistance.

In this study, the batch of patients was represented by 257 persons, hypertensive and with normal blood pressure, in whom we followed the evolution of the aortic stiffening, in correlation with the used medication, the compliance to the treatment, and the way of administrating the medication by the patient. The used treatment was represented by association of an angiotensin conversion enzyme inhibitor with diuretic, and association of an angiotensin II receptor antagonist with diuretic. From the gender distribution of the patients, we note the predominance of women (60%), compared to only 40% represented by men.

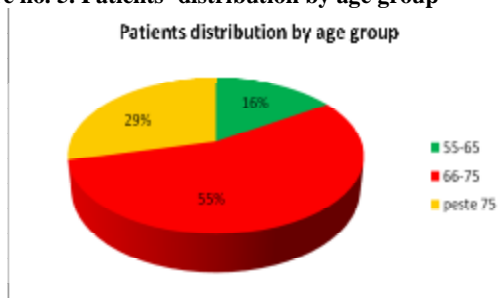
CLINICAL ASPECTS

Figure no. 4. Patients' distribution according to gender



The study batch was represented by old patients, men with an age of over 55 years, and women with an age of over 65 years. We split the batch in three categories, noting that the most patients are from the group with ages between 66 and 75 years old (55%).

Figure no. 5. Patients' distribution by age group



In our study batch, we had 10% of patients with normal blood pressure. The hypertensive patients group was split according to the medication they used. The first group was using a combination of ACEI+D (angiotensin conversion enzyme inhibitor and diuretic), and the second group ARA+D (angiotensin II receptor antagonist and diuretic). The patients were divided in two groups, depending on the way they administrated the medication:

- the ones observing the daily treatment schedule (continuous treatment)
- the ones following an incorrect treatment, taking their medication only when their blood pressure increased above the normal values (discontinuous treatment)

Figure no. 6. Patients' distribution by blood pressure values

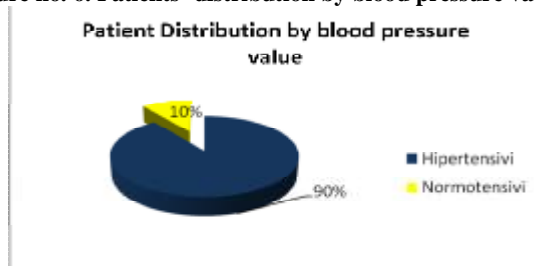


Figure no. 7. Distribution of hypertensive patients with ACEI+D according to the way the medication was administered

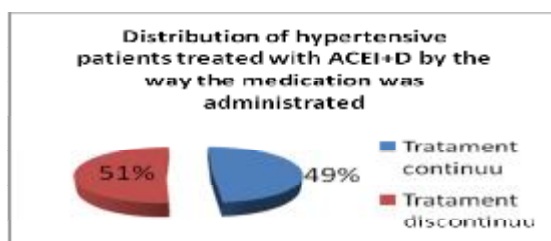
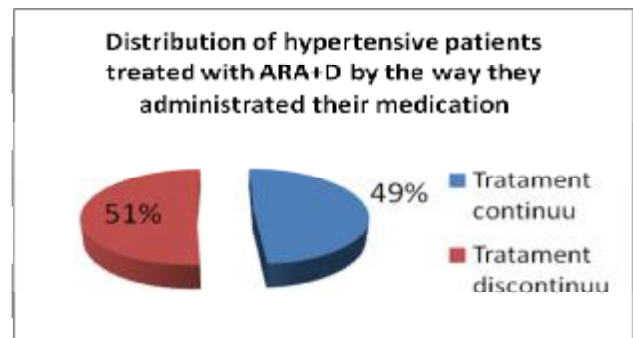


Figure no. 8. Distribution of hypertensive patients with ARA+D according to the way the medication was administered

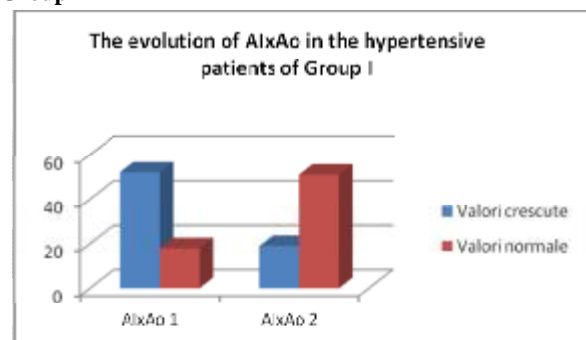


For an easier statistical interpretation, the patients were divided in four groups:

- Group I – discontinuous treatment with ACEI+D
- Group II – continuous treatment with ACEI+D
- Group III – discontinuous treatment with ARA+D
- Group IV – continuous treatment with ARA+D

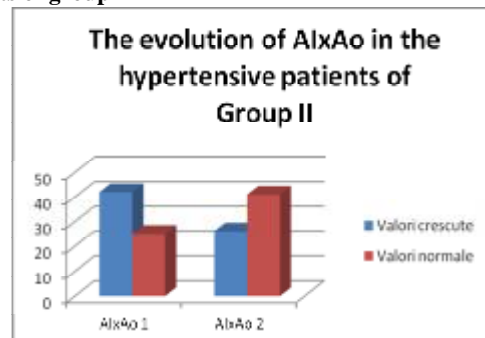
The measurements of the aortic stiffening indices were performed within a 6-month period of time with a device called arteriograph. I followed AIXAo and PWVAo as aortic stiffening indices. The increased values of these indicated a higher level of aortic stiffening, determined by the increase of the peripheral vessel resistance, by an endothelial dysfunction and by a decrease of the vascular elasticity.

Figure no. 9. Evolution of AIXAo in the hypertensive patients of Group I



It can be noticed the high percentage of patients with high level of aortic stiffening, which is reduced after 6 months of correctly administrated antihypertensive treatment.

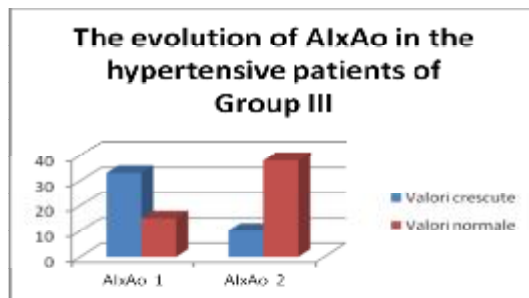
Figure no. 10. Evolution of AIXAo in the hypertensive patients of group II



It can be noticed that the percentage of normal AIXAo is much higher in those patients who follow correctly the

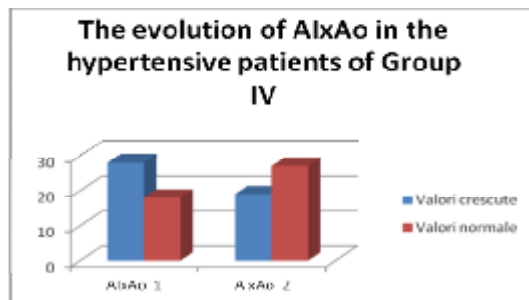
antihypertensive treatment scheme. In this group, we noticed a lower percentage of aortic stiffening.

Figure no. 11. Evolution of AIxAo in the hypertensive patients of group III



As in the first group of patients, an incorrect antihypertensive treatment leads to increased aortic stiffening, influenced by a correct administration of medication.

Figure no. 12. Evolution of AIxAo in the hypertensive patients of group IV

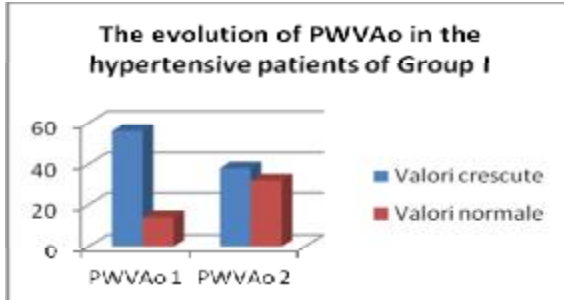


Compared to the third group, the correct administrated antihypertensive medication determines a lower grade of aortic stiffening.

PWVAo is influenced by the elasticity of the Aorta, which decreases with age, due to the reduction of elastin fibres.

In the older hypertensive patients, the increased value of PWVAo is due to both hypertension and age.

Figure no. 13. Evolution of PWPVAo in the hypertensive patients of group I



An incorrect treatment leads to an increase of the pulsed wave's velocity, prejudicing the arterial elasticity. The correction of the administration way of the medication leads to an amelioration of the arterial elasticity.

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Figure no. 14. Evolution of PWVAo in the hypertensive patients of group II

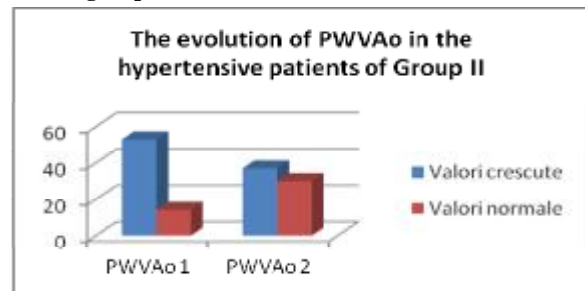


Figure no. 15. Evolution of PWVAo in the hypertensive patients of group III

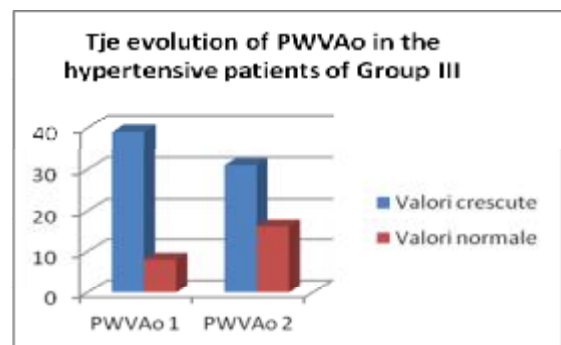
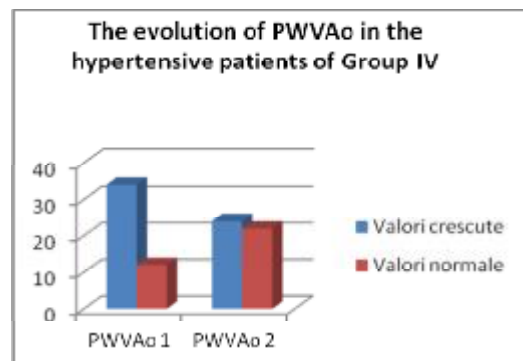


Figure no. 16. Evolution of PWVAo in the hypertensive patients of group IV



We can draw some conclusions concerning the benefits of antihypertensive treatment in the elderly patients. A correct treatment leads to a decrease of the aortic stiffening (a cardiovascular risk factor), with the amelioration of its elasticity, therefore having a favourable influence upon the cardiovascular morbidity and mortality.

Only one third of all hypertensive patients with apparently therapeutically controlled hypertension are protected from a stroke or a myocardial infarction (30) and only 20% from the elderly patients with isolated systolic arterial hypertension reach the target values of antihypertensive treatment. These data bring to our attention the fact that there are therapy goals in arterial hypertension which go beyond only reducing the values of the blood pressure in the brachial artery, as for example the amelioration of the aortic stiffening indices. Therefore, maybe, some authors called the central arterial blood pressure as being the "missing link" of the therapy goal in the case of the arterial pressure and they compared the investigation of adequate solutions for reducing the arterial stiffening with "searching for the Holy Grail".(31)

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