

EVALUATION THROUGH ARTERIOGRAPHY MEASUREMENTS OF THE EFFECTS OF IECA+D TREATMENT COMPARED TO THE BRA+D ONE ON THE DETERMINING PARAMETERS OF THE ARTERIAL FUNCTION (SBPAO, PWVAO, AIXAO) IN THE ELDERLY

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Abstract: Clinic research has shown that isolated systolic arterial hypertension (HTAS) more frequently encountered in the elderly, is characterised by a process of stiffening of the big vessels due to the deterioration of the elastic tissue from the medium tunic replaced by collagen fibres.(1,2) From a hemodynamic point of view, the stiffening of the aorta leads to a growing of the pulse wave velocity (PWV) and of the augmentation index (AIx) at the central level.(3,4) The vascular rigidity (the stiffness) appears before atherosclerosis irrespective of the classical risk factors. The examination of the arterial stiffness has been included in the ESH/ESC 2007 Guides regarding the management of the arterial hypertension.(5) It has been demonstrated that the medicines with an effect on the rennin-angiotensin-aldosterone system, in other words IECA and BRA, are in fact the most efficient medicine class in the case of lowering the arterial stiffness. More than that, in some cases this effect is more outstanding than the effect of lowering the arterial tension.(6)

Cuvinte cheie: PWV, Aix, rigidizare aortică, IECA, BRA, hipertensiune vârstnic

Rezumat: Date de cercetare clinică au evidențiat că hipertensiunea arterială sistolică izolată (HTAS) întâlnită mai frecvent la pacientul vârstnic, este caracterizată 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 undei de puls (PWV) și la creșterea indicelui de augmentare (AIx) la nivel central.(3,4) Rigiditatea vasculară (stiffness-ul) apare înaintea aterosclerozei, iar apariția acesteia poate fi privită ca un factor de risc a aterosclerozei, independent de factorii de risc clasici. Examinarea stiffness-ului arterial a fost inclusă în Ghidurile ESH/ESC 2007 de management a hipertensiunii arteriale.(5) S-a demonstrat că medicamentele cu efect asupra sistemului renină-angiotensină-aldosteron, cu alte cuvinte IECA și BRA, alcătuiesc cea mai eficientă clasă de medicamente în ceea ce privește scăderea stiffness-ului arterial, mai mult, în unele cazuri acest efect este mult mai marcant decât efectul de scădere a tensiunii arteriale.(6)

The evaluation of the arterial function through non-invasive methods currently uses the measurement of the parameters of the arterial function with the help of the arteriograph TensioMed; the propagation speed of the pulse wave in the aorta (PWVAo), the aortic augmentation index (AixAo) and the central systolic pressure (SBPAo). The aortic stiffness has a predictive value independent of the mortality of any cause and of the cardiovascular mortality, of the fatal and non-fatal coronary events and of the fatal cerebral stroke in HTA essential (7-9), in the case of diabetes (10), in the patients suffering of terminal chronic renal disease (11,12), in the elderly (13-14) and in the general population.(15-17) While the AixAo follows the endothelial dysfunction and the growth of the peripheral resistance (TPR) that it produces (it indicates atherosclerosis in very incipient phases), the PWVAo, which is related to the stiffness or the elasticity of the aortic wall, indicates a more advanced phase of the atherosclerosis. By measuring the stiffness parameters, we receive prognosis information concerning late cardiovascular events, such as the coronary atherosclerosis.

The TensioMed arteriograph measures the arterial stiffness parameters, thus being an optimal instrument for

screening examinations made with a diagnostic aim, as well as for the examinations of the therapeutic efficiency evaluation.

The central systolic pressure (SBPAo) is the arterial pressure measured close to the heart, in the aorta root. It does not have the same value with the pressure measured at the periphery (the brachial artery) because of the influence of the arterial stiffness and of the waves' reflexion. The high central pressure, even in the patients with a normal brachial pressure, is associated with a bigger vascular stroke risk, infarction and chronic renal disease, since this is the pressure that transposes itself without attenuation on the cerebral circulation, increases the after-load determining left ventricular hypertrophy.(18) The CAFE study, a part of the ASCOT study draws our attention upon a significant correlation between SBPAo dependent on the augmentation index and the cardiovascular events.(19,20) The central pressure non-invasively measured has a better predictive value than the arterial tension measured on the brachial artery.(21)

The determination of the pulse wave velocity is accepted as being the most simple and non-invasive method used to determine the arterial stiffness. The more rigid is the arterial wall the more velocity the pulse wave has. The lost of

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aorta elasticity, the developing of a high aortic stiffness, (signalled by an increasing PWVAo) is an important cardiovascular mortality predictor at the level of the average population. The limit between the normal/increased PWVAo value is determined through statistic methods (the ROC curve): this is given by the intersection point where both the sensitiveness and the specificity have the best values. Through this method, the limiting value is 9,62m/s for both sexes, more exactly values above this one mean increased PWVAo values.

The increased velocity of the pulse wave is added on the list of the factors that influence the prognostic as a precocious index of the big vessels stiffness.(22,23) The incipient phase of the atherosclerosis means endothelial dysfunction, with a reduction in the production of nitrogen monoxide (NO), with an increase of the vascular tonus and implicitly a peripheral vasoconstriction.(24) The bigger the Aix value the bigger the peripheral vascular resistance (TPR). The augmentation index mirrors and measures the arterioles real capacity of dilatation, offering information regarding their function or dysfunction, being modifiable through medication. The augmentation index is significantly correlated with cardiovascular events.(19) We have assessed the modification of the arterial function parameters SBPAo, PWVAo, AixAo on 257 old patients, randomly divided according to the treatment they used, within a 12 months period. Group I consisted of 137 hypertensive patients treated with the fix combination of IECA+D (conversion enzyme inhibitor and diuretic); group II consisted of 95 hypertensive patients treated with the fix combination BRA+D (blockers of angiotensin receptors and diuretic) and the witness group consisted of 25 normo-tensive patients. The age of the patients ranged between 55 and 97 years old, with an average of 77 years old. In group I, there were 84 women (61,31%) and 53 men (38,69%); group II consisted of 53 women (55,79%) and 42 men (44,21%) and the witness group was composed of 18 women (72%) and 7 men (28%).

The level of the arterial hypertension has been assessed according to the Hypertension European Society as follows:

Stage I – easy–Tas/Tad:140/90 mmHg – 159/99 mmHg

(Tas=systolic arterial tension; Tad=diastolic arterial tension)

Stage II – moderate –Tas/Tad:160/100 mmHg – 179/109 mmHg

Stage III – severe –Tas/Tad over 180/110 mmHg

Isolated systolic HTA - Tas>140 mmHg and Tad<90 mmHg (25)

After analysing the tensional values, I have noted that at the beginning of the study, in group I, 28 subjects could be placed in grade I of HTA (20,4%), 20 in grade II (14,6%), 3 in grade III (2,2%) and 86 subjects had HTAS (62,8). In group II, 21 subjects could be placed in grade I HTA (22,1%), 8 in grade II (8,4%), 3 in grade III (3,2%) and 63 subjects had HTAS (66,3%). We have measured the SBPAo, PWVAo, AixAo with the TensioMed arteriograph in both groups of patients as well as in the witness group at the beginning of the study and after 12 months. There were no significant statistic differences between the two groups from the point of view of age and sex distribution. The statistic testing of the differences between the groups submitted to research continued on the initial values of the SBPAo, PWVAo, AixAo. The testing was done with the help of test T for independent samples. The results obtained after implementing this test may be observed with the help of the SPSS 21 programme.

Table no. 1. The average values, the standard deviations and the initial standard errors on the two groups of SBPAo, PWVAo and AixAo

Group Statistics					
	Loturi	N	Mean	Std. Deviation	Std. Error Mean
presiunea sistolica centrala_initial	Lotul ACEI.D	137	145.289	22.7598	1.9445
	Lotul BRAD	95	143.736	17.3676	1.7819
indice de augmentatie aortica_initial	Lotul ACEI.D	137	38.899	10.8297	.9252
	Lotul BRAD	95	38.275	9.2477	.9488
viteza de circulatie a undei de puls_initial	Lotul ACEI.D	137	10.791	1.3789	.1178
	Lotul BRAD	95	10.619	1.4950	.1534

Table no. 2. The statistic independence test T on the two groups for the initial values of SBPAo, PWVAo and AixAo

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	99% Confidence Interval of the Difference	
									Lower	Upper
presiunea sistolica centrala_initial	Equal variances assumed	1.283	.257	.561	230	.575	1.5533	2.7672	-5.6342	8.7407
	Equal variances not assumed			.589	227.851	.556	1.5533	2.6375	-5.2977	8.4043
indice de augmentatie aortica_initial	Equal variances assumed	1.180	.278	.457	230	.648	.6238	1.3635	-2.9178	4.1654
	Equal variances not assumed			.471	220.171	.638	.6238	1.3253	-2.8197	4.0673
viteza de circulatie a undei de puls_initial	Equal variances assumed	.736	.392	.304	230	.367	.1723	.1906	-.3227	.6673
	Equal variances not assumed			.391	191.547	.374	.1723	.1934	-.3309	.6785

Since the testing was made on a confidence level of 99%, we can say, based on the above results, that we have to accept the null hypothesis, that is between the two groups there are no differences from the point of view of the three studied parameters. Looking at the last colons that contain the confidence interval for the averages differences, we observe that all these intervals contain the value 0, therefore it is possible that the averages difference to be zero and the averages to be equal.

In conclusion, the null hypothesis can be accepted which means that at the beginning of the study, the values of SBPAo, PWVAo and AixAo in the two groups were not significantly different. We should therefore, note that the treatment was applied to similar groups from the point of view of the composition of the three studied values.

Table no. 3. The statistic independence test T on the two groups for the final values of SBPAo, PWVAo and AixAo (implemented on SPSS 21)

Hypotheses Test Summary			
	Null Hypothesis	Test Statistic	Significance
1	The distribution of central systolic pressure is the same across categories of Groups.	15.1	Reject the null hypothesis.
2	The distribution of aortic augmentation index is the same across categories of Groups.	0.000	Reject the null hypothesis.
3	The distribution of pulse wave velocity is the same across categories of Groups.	0.000	Reject the null hypothesis.

1. The distribution of the central systolic pressure –finally is the same across categories of Groups.
2. The distribution of the aortic augmentation index – finally is the same across categories of Groups.
3. The distribution of the pulse wave velocity –finally is the same across categories of Groups.

Test T allows us to retain the null hypothesis for all the parameters taken into account. In order to see if the two treatments had the expected effects, we have used the

contingence table, i.e. we have followed in the two groups the initial and the final values for the three parameters. To do this, we have also used the SPSS 21 programme, the option cross tabs (association). We have built up an impact indicator to assess the global impact of the medicine on the two groups.

$$I_x = (1-r) \times 100$$

Where: x – the parameter whose values are improved between the initial and the final moment

r – Pearson correlation coefficient

We mention that previously the values of the parameters, both for the initial and for the final moment, were transformed in such a way that for each parameter we have the values: low, average and high.

For group I, we have calculated the impact on the three parameters:

- on SBPAo it is $I_{SBPAo} = (1-r) \times 100 = (1-0,623) \times 100 = 36,7\%$
- on PWVAo it is $I_{PWVAo} = (1-r) \times 100 = (1-0,412) \times 100 = 58,8\%$
- on AixAo it is $I_{AixAo} = (1-r) \times 100 = (1-0,473) \times 100 = 52,7\%$

For group I, we have calculated the normalised values with the ones in the witness group and the impact indicator looks as follows:

$$I'_x = [(1-r_x) / r_{x \text{ witness group}}] \times 100$$

Thus, the normalised values for group I are:

- on SBPAo it is $I'_{SBPAo} = [(1-r_x) / r_{x \text{ witness group}}] \times 100 = (0,367 / 0,745) \times 100 = 49,26\%$
- on PWVAo it is $I'_{PWVAo} = [(1-r_x) / r_{x \text{ witness group}}] \times 100 = (0,588 / 0,588) \times 100 = 100\%$
- on AixAo it is $I'_{AixAo} = [(1-r_x) / r_{x \text{ witness group}}] \times 100 = (1-0,473) \times 100 = 70,1\%$

We can therefore, say comparatively that the values for all the three parameters have improved (a great part of the high values have become normal), but most of all have improved the values of the circulation velocity of the pulse wave, then those of the index of aortic augmentation and then those of the central systolic pressure.

For group II, we have calculated the impact on the three parameters:

- on SBPAo it is $I_{SBPAo} = (1-r) \times 100 = (1-0,689) \times 100 = 31,1\%$
- on PWVAo it is $I_{PWVAo} = (1-r) \times 100 = (1-0,409) \times 100 = 59,1\%$
- on AixAo it is $I_{AixAo} = (1-r) \times 100 = (1-0,447) \times 100 = 55,3\%$

For group II, we have also calculated the normalised values with the ones in the witness group and the impact indicator looks as follows:

$$I'_x = [(1-r_x) / r_{x \text{ witness group}}] \times 100$$

Thus, the normalised values for group II are:

- on SBPAo it is $I'_{SBPAo} = [(1-r_x) / r_{x \text{ witness group}}] \times 100 = 41,7\%$
- on PWVAo it is $I'_{PWVAo} = [(1-r_x) / r_{x \text{ witness group}}] \times 100 = 100\%$
- on AixAo it is $I'_{AixAo} = [(1-r_x) / r_{x \text{ witness group}}] \times 100 = (1-0,473) \times 100 = 73,61\%$

Comparing the normalization percent of the values of the SBPAo parameters in the two groups we can sustain the fact that the influence of the two therapeutic groups is similar, without significant statistic differences (according to the statistic

significance test T). The different impact on the three parameters in both groups is, however, significant, the circulation velocity of the pulse wave and the aortic augmentation index being faster improved than the central systolic pressure. We therefore, witness a real improvement in the capacity of dilatation of the arterioles and in the reduction of the aorta stiffness, as a first effect of the anti-hypertensive medication (the effect of reduction of the peripheral vascular resistance of the medicines that have the effect of blocking the rennin-angiotensin system). In the end, we wanted to discover the differences on the three parameters between the research groups and the witness one. With that end in view, we have used the signification tests for independent samples (T) and the statistical programme SPSS 21.

Table no. 4. The statistical independence test T between the research groups and the witness group for the final values of SBPAo, PWVAo and AixAo (implemented on SPSS)

Hypothesis Test Summary			
Null Hypothesis	Test	Sig.	Decision
1 The distribution of the central systolic pressure is the same across categories of research groups	One-Sample T-Test	.000	Reject the null hypothesis
2 The distribution of the aortic augmentation index is the same across categories of research groups	One-Sample T-Test	.000	Reject the null hypothesis
3 The distribution of the pulse wave velocity is the same across categories of research groups	One-Sample T-Test	.000	Reject the null hypothesis
4 The distribution of the central systolic pressure is the same across categories of research groups	One-Sample T-Test	.000	Reject the null hypothesis
5 The distribution of the aortic augmentation index is the same across categories of research groups	One-Sample T-Test	.000	Reject the null hypothesis
6 The distribution of the pulse wave velocity is the same across categories of research groups	One-Sample T-Test	.000	Reject the null hypothesis

Significance levels are displayed. T = significance level is .05.

The distribution of the central systolic pressure – initially is the same across categories of research groups.

1. The distribution of the central systolic pressure – finally is the same across categories of research groups.
2. The distribution of the aortic augmentation index – initially is the same across categories of research groups.
3. The distribution of the aortic augmentation index – finally is the same across categories of research groups.
4. The distribution of the pulse wave velocity – initially is the same across categories of research groups.
5. The distribution of the pulse wave velocity – finally is the same across categories of research groups.

The conclusion we can draw from table no. 4 is that the null hypothesis is accepted for the initial values of SBPAo, PWVAo and AixAo (which confirms once more the correctness of the choice of the three groups, the witness group being composed of normo-tensive patients, thus having SBPAo, PWVAo and AixAo values significantly different from the ones of those patients having HTA) and that in two situations, for final values of PWVAo and AixAo, the value distribution is similar between the normo-tensive old patients and those with

HTA. We observe that at the end of the study, the PWVAo and AixAo values are closest to the ones of the witness group which proves that a well applied treatment influences positively the aortic stiffness and the peripheral vascular resistance. We mention that at the end of the study in group I 44,5% of the patients could be placed in grade I of HTA, 0,7% in grade II, 0,7% in grade III and 54% presented isolated systolic arterial hypertension; in group II, 45,3% of the patients could be placed in grade I of HTA, 1,1% in grade II and 53,7 % presented isolated systolic arterial hypertension.

As a conclusion, positive effects of the treatment within the two therapeutic groups could be observed on all the parameters of the arterial function that were taken into account in the study, more evident being the effects of improvement of the arterial stiffness compared to those that influence the values of the central systolic pressure.

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