EFFECTS OF ALISKIREN ON BLOOD PRESSURE AND MYOCARDIAL FUNCTION ASSESSED BY GLOBAL LONGITUDINAL STRAIN IN PATIENTS WITH ARTERIAL HYPERTENSION AND DIASTOLIC DYSFUNCTION

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ABSTRACT
OBJECTIVE: To evaluate the effects of aliskiren on blood pressure and myocardial function assessed by global longitudinal strain in patients with uncontrolled arterial hypertension.

PATIENTS AND METHODS: Forty-five patients were included in the study (29 males, 16 females, mean age 58.7 ± 12.4 years) with BP > 140/90 mmHg despite treatment with combined antihypertensive therapy and echocardiographic data for diastolic dysfunction: E/E’ ratio ≤ 8, E/A ratio < 0.8, deceleration time (DT) > 200 msec. Aliskiren (2 x 150 mg per day) was added to the previous therapy. The follow-up period was 1 year, including monthly clinical visits. Echocardiographic assessment of the left ventricular function by longitudinal strain and Doppler analysis of the trans-mitral blood flow was performed at months 1, 6, 12.

RESULTS: The baseline systolic and diastolic blood pressures scores were 153.4 ± 14.4/99.2 ± 6.7 mmHg and 157.6 ± 12.5/97.3 ± 8.2 mmHg for males and females, respectively. The systolic and diastolic values at 1 month were 131.7 ± 7.4/83.6 ± 5.2 mmHg for males and 132.4 ± 5.3/81.8 ± 6.9 mmHg for females (p < 0.05 vs. baseline). The baseline E/E’ was 6.5 ± 0.9, E/A - 0.6 ± 0.01, DT - 258 ± 32.7 msec. These indicators at month 12 were as follows: E/E’ - 7.0 ± 0.64, E/A - 0.7 ± 0.05, DT - 239 ± 16.5 msec, p = NS. Baseline global longitudinal strain in males was -10.4 ± 0.7% and -11.0 ± 0.9% in females and at month 12 - 16.3 ± 0.9% and -17.5 ± 0.7% for males and females, respectively, p < 0.05. For the period of follow-up no adverse effects due to aliskiren treatment were registered.

CONCLUSIONS: Adding aliskiren to combined antihypertensive therapy leads to significant improvement of hypertension control and myocardial function assessed by global longitudinal strain.

Key words: aliskiren, arterial hypertension, diastolic dysfunction, strain

INTRODUCTION
Arterial hypertension (AH) is an important cardiovascular risk factor worldwide.1,2 Despite the large choice of available antihypertensive drugs, the control of AH is quite insufficient and the majority of hypertensive patients do not reach the target values of blood pressure (BP).1-3 The major classes of first choice drugs for AH treatment are: inhibitors of angiotensin-converting enzyme (ACE-i), angiotensin II type 1 receptor blockers (ARB), thiazide or thiazide-like diuretics, calcium channel blockers (CCB) and beta blockers (BB). They are suitable for initiation and continuation of AH therapy, alone or in combinations.4-6

Direct renin inhibitors (DRI) are a new therapeutic option for hypertensive patients and aliskiren is the only representative of this class that has been approved for clinical use so far.2,3,7 Their antihypertensive effect is due to a specific blockage of the catalytic center of renin which they bond to with high affinity. Thus, the first and rate-limiting stage of renin-angiotensin-aldosterone cascade, the conversion of angiotensinogen into angiotensin I, is inhibited.2,5,8

In patients with cardiovascular diseases, including AH, diagnostic approach includes noninvasive assessment of myocardial function to determine the degree of the morphological changes, therapeutic behavior, early and long-term clinical prognosis.9-11 Tissue Doppler-echocardiography is an advanced echocardiographic (Echo) method for evaluation of myocardial function.9,11 This technique allows both
visual and quantitative interpretation of regional tissue velocity, strain, displacement and acceleration throughout the cardiac cycle in one image. The term “echocardiographic strain” is used to describe the regional deformation occurring in the myocardium during the cardiac cycle (myocardial extension, shortening, thickening). The high temporal and velocity resolution allows evaluation of the rapid movements during the systolic and diastolic isovolumetric period. Analysis of the isovolumetric velocity and acceleration characteristics during the assessment of global systolic and diastolic changes allows evaluation of the elastic, contractile properties of myocardium. The image of the movement of tissue obtained from the integral of tissue velocity curve along the longitudinal axis is presented as a time-dimensional color map of the movement of the myocardium during the cardiac cycle.

AIM

Evaluation of the effects of aliskiren on blood pressure (BP) and myocardial function assessed by global longitudinal strain in patients with uncontrolled arterial hypertension (AH).

PATIENTS AND METHODS

A prospective study including 45 consecutive patients with essential arterial hypertension - 29 males and 16 females, mean age 58.7 ± 12.4 (44-69) years. These patients had insufficient control of BP (> 140/90 mmHg) according to the current guidelines despite treatment with combined antihypertensive therapy, including some of the following classes of antihypertensive drugs: inhibitors of the angiotensin-converting enzyme (ACE-i), angiotensin II type I receptor blockers (ARB), calcium channel blockers (CB) and thiazide or thiazide-like diuretics. All patients had echocardiographic (Echo) data for diastolic function. Echocardiographic (Echo) data for diastolic dysfunction I degree according to 2009 EAE/ASE criteria: E/E’ ratio ≤ 8, E/A ratio < 0.8, deceleration time (DT) > 200 msec. The cardiovascular risk of the patients was assessed as mild to moderate according to the current ESC/ESH Guidelines for evaluation and treatment of arterial hypertension. The exclusion criteria were high cardiovascular risk as well as patients with secondary hypertension. Aliskiren 2×150 mg per day was added to the previous therapy. The follow-up period was 1 year, including monthly clinical visits. The blood pressure of the non-dominant arm was measured three times with 5-min intervals between measurements in a seated position after initial 15-min rest using a validated aneroid sphygmomanometer. The average of three BP measurements was used in the study. At each follow-up visit the patients were asked if they experienced any adverse effects of the treatment with aliskiren. Echocardiographic assessment of the left ventricular function by longitudinal strain in the grey scale and Doppler analysis of the trans-mitral blood flow was performed at months 1, 6 and 12. All patients signed an informed consent form before inclusion in our study.

Statistical analysis of the data was conducted using SPSS 13.0 for Windows. We used the following statistical methods:

A. Descriptive statistics: 1. Mean, standard deviation, minimum, maximum; 2. Frequency analysis (nominal and ranks) - absolute and relative frequencies (percentage).


As a level of significance we accepted p < 0.05.

RESULTS

The baseline systolic (SBP) and diastolic (DBP) blood pressure for the study sample were 153.4 ± 14.4 (142-168) / 99.2 ± 6.7 (93-104) mmHg for males and 157.6 ± 12.5 (147-172) / 97.3 ± 8.2 (92-106) mmHg for females.

Aliskiren added to the previous antihypertensive therapy brought about a significant decrease of SBP and DBP in the follow-up period. All patients achieved the target levels of BP < 140/90 mmHg within the first month of follow-up – 131.7 ± 7.4 (126-138) / 83.6 ± 5.2 (72-87) mmHg for men and 132.4 ± 5.3 (124-137) / 81.8 ± 6.9 (71-86) mmHg for women, (p < 0.05 vs. baseline) (Figs. 1, 2)

Baseline ratio E/E’ was 6.5 ± 0.9, and after 6 months – 6.6 ± 0.7 and after 12 months -7.0 ± 0.64, p = NS (Fig. 3).

Baseline ratio E/A was 0.6 ± 0.01, at 6 months - 0.6 ± 0.04 and at 12 months – 0.7 ± 0.05, p = NS (Fig. 4).

Baseline mean values of DT were 258.4 ± 32.7 msec, at 6 months – 246.2 ± 22.4 msec and at 12 months of follow-up – 239.0 ± 16.5 msec, p = NS (Fig. 5).

Baseline echocardiographic strain in males was -10.4 ± 0.7% and in females -11.0 ± 0.9%. The strain at 6 months was -12.3 ± 1.1% and -13.2 ± 1.4% for males and females, respectively and at 12 months -16.3 ± 1.5% and -17.5 ± 1.8%, p < 0.05 compared to baseline (Fig. 6).

Treatment with aliskiren was well tolerated by
patients. For the period of clinical observation no side effects and discontinuation of therapy by patients was has been registered.

**DISCUSSION**

A serious problem facing modern cardiology is the inadequate compliance and persistence of the majority of patients on antihypertensive therapy.\(^1\,^2\) Some of the widely discussed reasons for this phenomenon are side effects of conventional antihypertensive medication, lack of adequate therapeutic response and adulterate contact between doctors and patients.\(^1\,^8\) In this respect, implementation of a new antihypertensive class of drugs is encouraging.\(^13\) Aliskiren (Rasilez\(^\text{®}\)) is a direct renin inhibitor whose effect is realized by binding with high affinity and specificity to the catalytic site of renin, thereby inhibiting the first rate-limiting step of the renin-angiotensin-aldosterone system (RAAS), namely the conversion of angiotensinogen to angiotensin I.\(^7\,^8\) Although it is a novel agent, the therapeutic effects of aliskiren were tested in many randomized clinical trials with a variety of indications. The study AGEELESS demonstrated the superiority of antihypertensive effect of aliskiren compared to ramipril with a similar safety profile and significantly lower rates of cough as a side effect.\(^2\) ALOFT program provided strong evidence that aliskiren significantly reduced levels of BNP and NT-proBNP compared with placebo in patients with heart failure to conventional therapy.\(^3\)
The effect of the direct renin inhibitor on morbidity and mortality has been studied in patients with diabetic nephropathy (ALTITUDE), patients with heart failure (ATMOSPHERE), compensated patients, hospitalized for acute heart failure (ASTRONAUT), as well as in adults (APOLLO).2

Because the effect of aliskiren on patients with uncontrolled hypertension and diastolic dysfunction compared to combination therapy has not been studied, we aimed to investigate its effect on BP and on global myocardial function.14-16 We examined and followed up the Doppler-echo parameters of trans-mitral blood flow, specifying diastolic function, and discrete changes in myocardial function investigated by global longitudinal strain. Adding aliskiren to antihypertensive therapy resulted in a significant decrease in SBP and DBP in the follow-up period. All patients achieved target levels of BP < 140/90 mmHg within the first month of follow-up – 131.7 ± 7.4 (126-138)/83.6 ± 5.2 (72-87) mmHg for men and 132.4 ± 5.3 (124-137)/81.8 ± 6.9 (71-86) mmHg for women. In all patients BP remained within the normal range during the follow-up of 1 year. It is essential that no side effects and adverse reactions were observed for this period in our group. Interestingly, although the changes in the indicators of diastolic dysfunction were statistically insignificant, myocardial function assessed by echocardiographic strain was reliably improved. The baseline GLS in men was -10.4 ± 0.7%, while in women -11.0 ± 0.9%. The strain at 6 months was -12.3 ± 1.1% and -13.2 ± 1.4% for men and women, respectively, while at 12 months -16.3 ± 1.5% and -17.5 ± 1.8%, p < 0.05 compared to baseline. These facts indicate that traditional Doppler-performance evaluation of diastolic function did not correlate with changes in global myocardial function. In this regard, echocardiographic longitudinal strain is a method with greater potential. The most likely reason for the observed beneficial effects of aliskiren on cardiac muscle function is the precise, reliable direct inhibition of the renin-angiotensin system - a key factor in the development of hypertension-related complications in all target organs. Experimental animal models of myocardial infarction have shown that aliskiren reduces left ventricular hypertrophy and has cardioprotective effects.2,6 There has been found a beneficial effect on markers of systolic and diastolic function even in insignificant change of BP.5,6 We did not find similar beneficial effect on diastolic function, probably because the follow-up period was short. The most probable reason for the observed positive effects that other authors discuss is the inhibition of metallo-proteinases by inhibition of the RAAS. These facts will be interpreted much more adequate after the final analysis of the ALOFT study (aliskiren study in post MI patient to reduce remodeling) is performed. Significant decrease in BNP and NT-proBNP in patients with HF, as illustrated in the study ALOFT (aliskiren Observation of Heart Failure Treatment) is evidence for the cardioprotective effect of aliskiren.2 Our results are consistent with the data of the ALOFT study and show that administration of aliskiren in patients with uncontrolled hypertension improves myocardial function assessed by echocardiographic longitudinal strain. According to literature data, however GLS about -12% correlates well with systolic dysfunction and LVEF about 35%.17 The baseline GLS values in our patients with diastolic dysfunction grade I and preserved global systolic function were similar. These data could be interpreted in light of the fact that there are still no standardized norms for GLS, as well as the subjectivity which is important factor in the implementation of the methodology. Despite the observed discrepancy, the important finding in our study is the statistically significant trend towards improvement of myocardial function assessed by GLS in the course of treatment with aliskiren.

CONCLUSIONS

The direct renin inhibitor aliskiren, added to standard therapy in patients with inadequately controlled hypertension and diastolic dysfunction leads to permanent stabilization of BP and improvement of myocardial function, having very good safety profile.

REFERENCES

ЭФФЕКТ МЕДИКАМЕНТА ALISKIREN НА АРТЕРИАЛЬНОЕ ДАВЛЕНИЕ И ФУНКЦИЮ МИОКАРДА, ОЦЕНЕННУЮ ПОСРЕДСТВОМ ЛОНГИТУДИНАЛЬНОГО STRAIN-А У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТОНИЕЙ И ДИСФУНКЦИЕЙ ДИАСТОЛЫ

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РЕЗЮМЕ

ЦЕЛЬ: Проследить воздействие медикамента Aliskiren на артериальное давление (АД) и функцию миокарда, оцененную посредством лонгитудинального strain-а у пациентов с неконтролируемой артериальной гипертонией (АГ).

МАТЕРИАЛ И МЕТОДЫ: В исследование включено 45 пациентов (29 мужчин и 16 женщин) в возрасте 58.7 ± 12.4 года; стоимости АД > 140/90 мм вод. ст. на фоне комбинированной антигипертензивной терапии; эхокардиографические (ЭхоКГ) и Doppler-данные о динамике диастолы I степени по критериям EAE/ASE от 2009 г.; соотношение E/E′ ≤ 8, E/A < 0.8, время декаплигации (DT) > 200 мсек. К терапии добавлен Aliskiren 2 х 150 мг в день. Период наблюдения 1 год – посещение в клинике раз в месяц. ЭхоКГ оценку левожелудочковой функции посредством лонгитудинального strain-а и Doppler-анализа трансмитрального кровотока проводили на 1, 6 и 12 мес.

РЕЗУЛЬТАТЫ: Исходные стоимости систолического и диастолического артериального давления в границах: 153.4 ± 14.4 / 99.2 ± 6.7 мм вод. ст. для мужчин и 157.6 ± 12.5 / 97.3 ± 8.2 мм вод. ст. для женщин. Стоимости АД на 1 мес. после включения медикамента Aliskiren следующие: 131.7 ± 7.4 / 83.6 ± 5.2 мм вод. ст. для мужчин и 132.4 ± 5.3 / 81.8 ± 6.9 мм вод. ст. для женщин, p < 0.05 по сравнению с начальными стоимостями, а именно: E/E′ 6.5 ± 0.9, E/A – 0.6 ± 0.01, DT – 258 ± 32.7 мсек.

Стоимости исследованных ЭхоКГ показателей на 12 мес.: E/E′ - 7.0 ± 0.64, DT – 239 ± 16.5 мсек, p = N.S.; Исходный глобальный лонгитудинальный strain (GLS) у мужчин – 10.4 ± 0.7%, а у женщин – 11.0 ± 0.9%. Глобальный лонгитудинальный strain, определен на 12 мес. – 16.3 ± 0.9% и 17.5 ± 0.7% для мужчин и женщин соответственно, p < 0.05. За время клинического наблюдения не было зарегистрировано побочных нежелательных реакций в результате лечения медикаментом Aliskiren.

ЗАКЛЮЧЕНИЕ: Добавление Aliskiren-а к комбинированной антигипертензивной терапии привело к значительному улучшению контроля за АГ и функцией миокарда, оцененной посредством глобального лонгитудинального strain-а. Лечение хорошо воспринято пациентами.