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Efficacy of bisoprolol use in heart failure patients depending on pharmacogenetic profile

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Objective. To investigate possible relationship between Arg389Gly and Ser49Gly gene polymorphisms of β_1-adrenoreceptors (β_1-AP) and cardiodynamic indices in patients with severe heart failure (HF) before and after the use of the standard bisoprolol therapy during 1 year.

Methods and materials. Investigation involved 99 patients (78 men and 21 women, mean age 61.7 ± 0.96 years) with chronic HF and systolic dysfunction. Determination of the types of β_1-AP gene polymorphism by two spot mutations (Ser49Gly and Gly389Arg) was performed with chain polymerase reaction. Echocardiographic and hemodynamic parameters, e.g. systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and cardiac rate were assessed at baseline and after one year. All patients received standard HF therapy with the use of bisoprolol.

Results and discussion. At the beginning of the study, there were no significant difference in the cardiac rate. whereas patients homozygous for the Arg389 allele, demonstrated higher SAP and DAP levels. After one year of the standard therapy with bisoprolol, the significantly evident reduction in SAP, DAP and cardiac rate were registered in the Arg389 carriers vs the patients homozygous for the Gly389 allele. The obtained data showed the effects of Ser49Gly and Arg389Arg genotypes β_1-AP on the left ventricular structure in patients with severe HF. It has been revealed that Arg389Arg gene polymorphism β_1-AP was associated with the significant reduction of the end-diastolic and — systolic dimensions, left ventricular mass index, increase of the left ventricular ejection fraction in comparison with the homozygous carriers of Gly389 allele.

Conclusions. Thus, the presence of Arg389 allele and Ser49Gly genotype can provide effects on the cardiodynamic indices in patients with severe HF.

Key words:
heart failure, pharmacogenetics, gene polymorphism β_1-adrenoceptor, beta-blockers, echocardiographic parameters, blood pressure.

КОНТАКТНА ІНФОРМАЦІЯ

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One of the reasons of high prevalence of systolic heart failure (HF) in the modern society is the increasingly number of myocardial infarction survived patients with left ventricular dysfunction. Recent studies have underlined the importance of neuro-hormonal alternations. The major determinants of the left ventricular dysfunction progression and poor outcomes of the HF patients is increased cardiac adrenergic drive, that's why beta-blockers play the key role in the treatment of such condition [9]. A meta-analysis of 22 placebo-controlled randomized β-blocker trials involving 10.132 patients with chronic systolic HF demonstrated an odds ratio for total mortality of 0.65 in favor of β-blocker use [2]. However, in clinical practice, there is heterogeneity in the response to these drugs and some of the patients did not receive advantages of β-blockers therapy. The recognition that individualized using of β-blockers is associated with significant decreased risk of mortality in HF patients, has prompted a search for pharmacogenetic mechanisms that mediate such association. Identifying those patients who will benefit from β-blockers therapy, which dose will be optimal for them without adverse events and time of titration remains the

current challenge. It is known that variability in the drug response can be determined by polymorphisms in the genes-target and in genes encoding enzymes and proteins biotransformation. Beta-adrenergic receptors (β-AR) single nucleotide gene polymorphisms may influence the sensitivity and density of β-AR and determine the response to beta-blockers therapy. The most two common nonsynonymous single nucleotide polymorphisms in β_1-AR at nucleotides 145 and 1165 (amino acid position 49 and 389). At position 49 in the amino terminus of the receptor a serine is substituted by a glycine. *In vitro* studies shown that the Gly49 variant of the β_1-AR shows enhanced susceptibility to agonist-induced down-regulation [5]. At position 389 in the proximal part of the carboxy terminus, a glycine is substituted by an agrinine. Mason et al., in the study with CHW cells, showed that the Arg389 variant exhibited higher basal and 3- to 4-fold higher isoproterenol-stimulated adenylyl-cyclase activity than the Gly389 variants as a result of a greater coupling of the Arg389 variant to the Gs protein [8]. Further work using nonfailing ventricular tissue has demonstrated a clear differences between β_1-AR variants, with Arg389 tissues having greater contractile responses that Gly389 tissues to isoproterenol [4]. Using rodent models, Ser49Gly polymorphism was a demonstrated significant difference in agonist-related down-regulation, with the Ser49 variant being more resistant. Levin et all presented the evidence that receptor coupling is also affected, with the Ser49 variant being less active [10, 11]. Despite that the strong evidences *in-vitro* were obtained regarding the functional differences in both β_1-AR polymorphisms, the data how they impact in real clinical practice is still controversy.

In fact, the majority of published studies demonstrated the influence of Arg389Gly and Ser49Gly β_1-AR gene polymorphisms on the beneficial effects of beta-blockers therapy for HF patients. Conflicting results have been reported for the association between β_1-AR gene polymorphisms and changes in LV function before and after beta-blocker treatment [7]. In respect to remodeling, homozygous Arg389 β_1-AR subjects it has been shown a greater increase in the LVEF compared with Gly389 carriers and also Gly49 allele carriers had a significantly greater reduction in left ventricular end diastolic diameter than Ser 49 homozygous in some studies and a meta-analysis, but not all [3, 6, 12].

Several studies have looked for possible effects of Ser49Gly or Arg389Gly β_1-AR gene polymorphisms on blood pressure and heart rate responses to beta-blockers treatment in hypertensive treatment but divergent results also have been obtained [1]. May be it can be determined by the heterogeneity inside the beta-blockers group or the differences between the patients' populations, so that's why the further studies are necessary. Father of pharmacogenomics, Arno Motulsky said: «...there will have to be more research before PGx can really be put into practice...».

Purpose — to study the possible influence of Arg389Gly and Ser49Gly β_1-AR gene polymorphism on cardiohaemodynamic parameters in patients with severe HF before and after taking bisoprolol during on year.

Materials and methods

Ninety nine patients (78 males and 21 females; mean age (61.7 ± 0.96) years) with chronic heart failure and systolic dysfunction were enrolled in the study. Genotyping was performed to identify the individual β_1-AR Arg389Gly and Ser49Gly polymorphism by the restriction fragment length analysis of polymerase chain reaction products. The echocardiographic parameters (left ventricular diastolic and systolic internal dimension (LVIDd and LVIDs), left ventricular end-diastolic and systolic volume (LVEDV and LVESV), left ventricular ejection fraction (LVEF)) were measured with M- and B-mode echocardiography using Ultrasound's Vivid Three with a 2.5-MHz probe (Japan) and calculated following the American Guidelines of Echocardiography Society. Left ventricular mass (LVM) was calculated as described by Devereux et al. Left ventricular mass index (LVMI) was obtained by dividing LVM on height. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were measured by a doctor on the arm of the patient in a seated position after a 15-min rest. The echocardiographic and hemodynamic parameters (SBP and DBP, HR) were measured at the beginning and after one year. All patients received standard therapy of heart failure using bisoprolol. Demographic, clinical and procedural data were collected and entered into a database. Data are expressed as median and interquartile range for continuous variables (25th, 75th percentile) or as percentages. For nonparametric comparisons Mann—Whitney U test was used. All statistical tests were 2-tailed and $p < 0.05$ was considered statistically significant. All patients signed informed consent to participate in the study. The study was approved by the local Ethics Committee.

Results and discussion

The characteristics of the patients are presented in Table 1.

In our study we assessed the prevalence of Ser49Gly β_1-AR polymorphism: Ser49Ser (homozy-

Table 1. Characteristics of patients

Characteristics	Parameters
Mean age (years), mean ± SD	61.7 ± 0.96
Sex (male/female), %	81.8/18.2
Cause of HF, coronary artery disease, %	100
Diabetes mellitus, %	33.3
Stable angina pectoris, %	90
Myocardial infarction, %	100
2 or more myocardial infarctions, %	14.9
NYHA II functional class, %	33.1
NYHA III functional class, %	62.8
NYHA IV functional class, %	4.1
BMI (kg/m^2)	30.7 (27.1 : 34.74)
Waist circumference (cm)	106 (96 : 115)
LVEF, %	39.2 (33.7 : 42.2)
SBP, mm Hg	150 (130 : 160)
DBP, mm Hg	90 (80 : 100)
HR, beats/min	78 (72 : 90)
Total cholesterol, mmol/l	4.9 (4.1 : 5.63)
Glycated hemoglobin (HbA_{1c})	5.9 (5.0 : 7.2)
HOMA-IR	3.5 (2.6 : 5.5)
C-reactive protein, mg/l	6.2 (4.0 : 8.3)
Tumor necrosis factor, pg/ml	5.3 (4.6 : 6.5)
Glomerular filtration rate (GFR)	97.6 (78.0 : 124.0)
Rating scale of clinical state, score	6.0 (4.0 : 8.0)
Quality of life, score	35 (32 : 41)

Table 2. Ser49Gly β_1-AR polymorphism and baseline haemodynamic variables (Me [LQ; UQ])

Parameters	Patients with Ser49Ser type of β_1-adrenergic receptor polymorphism (n = 82)	Patients with Ser49Gly type of β_1-adrenergic receptor polymorphism (n = 17)
SBP, mm Hg	149 (130 : 160)	150 (132 : 160)
DBP, mm Hg	90 (80 : 100)	100 (80 : 100)
HR, beats/min	78 (70 : 88)	73 (72 : 85)

Table 3. Arg389Gly β_1-AR polymorphism and baseline haemodynamic variables (Me [LQ; UQ])

Parameters	Patients with Gly389Gly genotype (n = 9)	Patients with Arg389Gly genotype (n = 42)	Patients with Arg389Arg genotype (n = 48)
HR, beats/min	72 (69 : 84)	76 (70 : 84)	78 (71 : 92)
SBP, mm Hg	140 (126 : 160)	139 (120 : 160)	153 (140 : 160)*
DBP, mm Hg	85 (80 : 100)	87 (80 : 100)	98 (82 : 100)*

* Statistical significance of variables between Arg389 homozygotes and Arg389Gly polymorphism carriers, p < 0.05.

gous wild-type) was found in 82 (82.8 %) patients, Ser49Gly (heterozygote) — in 17 (17.2 %) and we didn't have subjects with Gly49Gly (homozygous mutant) genotype. The overall prevalence of the second polymorphism, particularly three genotypes were Arg389Arg (homozygous wild-type) in 48 (48.5 %) patients, Arg389Gly (heterozygote) — in 42 (42.4 %) and Gly389Gly (homozygous mutant) in 9 (9.1 %) subjects. The genotype frequencies were in Hardy—Weinberg equilibrium.

Table 4. Echocardiographic variables in the heart failure patients according to the β_1-adrenergic receptor gene Ser49Gly polymorphism (Me [LQ; UQ])

Parameters	Patients with Ser49Ser type of β_1-adrenergic receptor polymorphism (n = 82)	Patients with Ser49Gly type of β_1-adrenergic receptor polymorphism (n = 17)
LVIDd, sm	6.2 (5.7 : 6.6)	6.8 (6.2 : 7.1)*
LVIDs, sm	4.9 (4.5 : 5.6)	5.6 (5.3 : 5.9)*
LVEF, %	39.6 (33.7 : 42.2)	33.0 (30.2 : 37.3)*

* Statistical significance of variables between Ser49 homozygotes and Ser49Gly polymorphism carriers, p < 0.05;

We found no evidences of an intermediate effect manifested as either HR or blood pressure differences related to Ser49Gly β_1-AR polymorphism, as indicated in Table 2.

As shown in the Table 3 no differences between β_1-adrenergic receptor Arg389Gly genotypes were found with respect of heart rates, but the highest SBP and DPB has been found in patients homozygous for the Arg389 β_1-adrenergic receptor.

The presents of Ser49Gly β_1-adrenergic receptor gene polymorphism at baseline was associated with significantly greater LVIDd and LVIDs increase and LVEF decrease in heart failure patients, Table 4.

The echocardiographic parameters in our study in three types of Arg389Gly β-AR polymorphism are listed in Table 5. Compared different types of Arg389Gly—AR polymorphism at baseline, we observed a significant increase of IVS and LVPW in homozygous Arg389 patients compared to the Gly 389 carriers ($p < 0.005$). The subjects with Arg389Arg genotypes of β-AR polymorphism shows increased LVMI value compared to the Gly389 homozygotes ($p < 0.005$). No differences in LVEF were found between these three groups.

After one year of HF standard therapy using bisoprolol treatment SBP, DBP and HR were improved compared with baseline in both group of Ser49Gly β_1-adrenergic receptor gene polymorphism ($p < 0.05$), Table 6.

In the group of Arg389Arg carriers the SBP and DBP were decreased from 153 (140 : 160) to 137 (130 : 150) mm Hg and from 98 (82:100) to 88 (82 : 94) mm Hg, respectively ($p < 0.05$). SBP was decreased from 139 (120 : 160) to 125 (116 : 145) mm Hg and DBP from 87 (80 : 100) to 82 (76 : 88) mm Hg in Arg389Gly carriers ($p < 0.05$). The decrease of SBP from 140 (126 : 160) to 136 (120 : 145) mm Hg and DBP from 85 (80 : 100) to 84 (78 : 94) mm Hg in the group of homozygous carriers of Gly389 didn't reach a significance

Table 5. Echocardiographic variables in the heart failure patients according to the Arg389Gly β_1-AR polymorphism, (Me [LQ; UQ])

Parameters	Patients with Gly389Gly genotype (n = 9)	Patients with Arg389Gly genotype (n = 42)	Patients with Arg389Arg genotype (n = 48)
IVS, sm	0.9 (0.8 : 0.9)	1.2 (1.1 : 1.2)	1.3 (1.2 : 1.3)*#
LVPW, sm	1.0 (0.8 : 1.0)	1.2 (1.1 : 1.2)	1.25 (1.2 : 1.4)*#
LVIDd, sm	6.3 (5.8 : 7.0)	6.1 (5.8 : 6.8)	6.2 (5.8 : 6.8)
LVIDs, sm	5.1 (4.8 : 5.6)	5.0 (4.5 : 5.7)	4.96 (4.7 : 5.7)
LVEF, %	37.8 (26.8 : 41.2)	37.9 (33.6 : 43.3)	38.8 (33.1 : 41.9)
LVMI, gr/m^2	127.7 (115.8 : 144.6)	160.9 (136.9 : 191.2)	175.3 (146.9 : 207.8)*

* Statistical significance of variables between Gly389 and Arg389 homozygotes, $p < 0.05$; #statistical significance of variables between Arg389 homozygotes and Arg389Gly polymorphism carriers, $p < 0.05$.

($p > 0.05$). The largest decrease in HR by 16.0 % (from 78 (71 : 92) to 65.5 (60 : 72) beats / min) was found in patients homozygous carriers of Arg389, whereas in the group of patients with genotype Arg389Gly reduce was 10.5 % (from 76 (70 : 84) to 68 (63 : 76) beats / min) ($p < 0.05$ for all values). In the group of Gly389Gly β_1-AR gene polymorphism the decrease in HR (from 72 (69 : 84) to 69 (66 : 88) beats/minute) didn't reach a significance ($p > 0.05$).

In one year, standard therapy of HF using bisoprolol was associated with significant improvements of echocardiographic variables and didn't depend on different types of Ser49Gly β_1-AR polymorphisms. However, LVIDs decrease and LVEF increase tended to be less in the homozygous Ser49S carriers than Ser49Gly patients (7.0 and 8.1 % comparing with 21.8 and 26.7 %, respectively), but it didn't reach a significance.

Interestingly, in the group of homozygous β_1Arg389 patients who received bisoprolol the LVIDd and LVMI were significant decreased from 6.2 (5.8 : 6.8) to 6.0 (5.4 : 6.2) sm and from 175.3 (146.9 : 207.8) to 149.1 (127.6 : 188.3) g/m^2, respectively ($p < 0.05$). LVIDs was decreased from 5.0 (4.7 : 5.7) to 4.7 (4.4 : 5.1) sm in homozygous carriers of Arg389 allele and from 5.0 (4.5 : 5.7) to 4.7 (4.1 : 5.3) sm in Arg389Gly subjects. LVEF was increased only in the Arg389Arg β_1-AR polymorphism carriers (from 38.8 (33.1 : 41.9) to 42.7 (33.5 : 46.5) %), ($p < 0.05$). In the group of Gly389Gly β_1-adrenergic gene polymorphism these changes didn't reach a significance, ($p > 0.05$).

Table 6. Dynamics of haemodynamic variables depending on Ser49Gly β_1-AR polymorphism (Me [LQ; UQ])

Parameters	Patients with Ser49Ser type of β_1-adrenergic receptor polymorphism (n = 82)	Patients with Ser49Gly type of β_1-adrenergic receptor polymorphism (n = 17)
SBP before treatment, mm Hg	149 (130 : 160)	150 (132 : 160)
SBP after treatment, mm Hg	135 (120 : 150)*	134 (125 : 140)*
DBP before treatment, mm Hg	90 (80 : 100)	100 (80 : 100)
DBP after treatment, mm Hg	84 (78 : 92)*	90 (80 : 96)*
HR before treatment, beats/min	78 (70 : 88)	73 (72 : 85)
HR after treatment, beats/min	68 (63 : 75)*	65 (61 : 70)*

* Statistical significance before and after treatment, $p < 0.05$.

Conclusions

The main finding of our study is the obvious impact of β_1-AR polymorphism on cardiohaemodynamic parameters in severe heart failure patients. At baseline no differences between β_1-AR Arg389Gly and Ser49Gly genotypes were found with respect of heart rates, but regarding to the level of blood pressure, the highest SBP and DPB has been found in patients homozygous for the Arg389 β_1-AR. It was observed that Arg389 carriers had a significantly greater reduction of SBP, DBP and HR than did patients homozygous for Gly389 β_1-AR after 1 year HF therapy using bisoprolol. .At baseline the Ser49Gly and Arg389Arg genotypes of β_1-AR shows an impact o the left ventricular structure in the patients with severe HF. The presents of Arg389Arg β_1-AR gene polymorphism was associated with significantly LVIDd, LVIDs and LVMI decrease, LVEF increase and SBP, DBP, HR improvement compared with Gly389 homozygous patients. In such context, pharmacogenetic factors, such as polymorphisms of β_1-AR may be one of the important part for prediction interindividual efficacy of β_1-blockers treatment in severe HF patients.

Perspective. Personalized medicine based on pharmacogenetic is impetuous involving and developing. Indeed, to move its results to clinical practice, future studies should be larger and have to consider the complexity of drug response.

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Ефективність використання бісопрололу в пацієнтів із серцевою недостатністю залежно від фармакогенетичного профілю

Мета роботи — дослідити наявність можливого зв'язку між Arg389Gly та Ser49Gly поліморфізмами гена β_1-адренорецепторів (β_1-АР) та кардіогемодинамічними показниками у пацієнтів з тяжкою серцевою недостатністю (СН) до та після застосування стандартної терапії з використанням бісопрололу протягом одного року.

Матеріали та методи. У дослідження було включено 99 пацієнтів (78 чоловіків та 21 жінка, середній вік (61,7 ± 0,96) року) із хронічною СН та систолічною дисфункцією. Поліморфізм гена β_1-АР за двома мутаціями (Ser49Gly і Gly389Arg) було визначено за допомогою полімеразної ланцюгової реакції. Ехокардіографічні та гемодинамічні параметри, такі як систолічний артеріальний тиск (САТ), діастолічний артеріальний тиск (ДАТ) та частота серцевих скорочень (ЧСС), були визначені до та після лікування протягом одного року. Усі пацієнти отримували стандартну терапію СН з використанням бісопрололу.

Результати та обговорення. На початку нашого дослідження статистично значущих відмінностей відносно ЧСС отримано не було, в той же час у пацієнтів, гомозиготних за Arg389 алелем, відзначалися більш високі рівні САТ та ДАТ. Через рік на тлі стандартної терапії з використанням бісопрололу було зареєстровано достовірно більш виражене зниження САТ, ДАТ та ЧСС у носіїв Arg389 у порівнянні з хворими, гомозиготними за Gly389 алелем. Отримані дані, що свідчать про наявність впливу Ser49Gly і Arg389Arg генотипів β_1-АР на структуру лівого шлуночка в пацієнтів з тяжкою СН. Визначено, що Arg389Arg тип поліморфізму гена β_1-АР асоціюється з достовірним зменшенням кінцеводіастолічного та систолічного розмірів, індексу маси лівого шлуночка, збільшенням фракції викиду лівого шлуночка у порівнянні з гомозиготними носіями Gly389 алеля.

Висновки. Таким чином, наявність Arg389 алеля та Ser49Gly генотипу може впливати на кардіогемодинамічні показники в пацієнтів з тяжкою СН.

Ключові слова: серцева недостатність, фармакогенетика, поліморфізм гена β_1-адренорецепторів, бета-адреноблокатори, ехокардіографічні показники, артеріальний тиск.

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Эффективность использования бисопролола у пациентов с сердечной недостаточностью в зависимости от фармакогенетического профиля

Цель работы — изучить наличие возможной связи между Arg389Gly и Ser49Gly полиморфизмами гена β_1-адренорецепторов (β_1-АР) и кардиогемодинамическими показателями у пациентов с тяжелой сердечной недостаточностью (СН) до и после применения стандартной терапии с использованием бисопролола в течение года.

Материалы и методы. В исследование было включено 99 пациентов (78 мужчин и 21 женщина, средний возраст (61,7 ± 0,96) года) с хронической СН и систолической дисфункцией. Определение типов полиморфизма генов β_1-АР по двум точечным мутациям (Ser49Gly и Gly389Arg) было выполнено с помощью полимеразной цепной реакции. Эхокардиографические и гемодинамические параметры, такие как систолическое артериальное

давление (САД), диастолическое артериальное давление (ДАД) и частота сердечных сокращений (ЧСС) были оценены в начале лечения и через один год. Все пациенты получали стандартную терапию СН с использованием бисопролола.

Результаты и обсуждение. В начале нашего исследования статистически значимых различий относительно ЧСС отмечено не было, в то же время у пациентов, гомозиготных по Arg389 аллелю, отмечались более высокие базальные уровни САД и ДАД. Через год на фоне стандартной терапии с использованием бисопролола зарегистрировано достоверно более выраженное снижение САД, ДАД и ЧСС у носителей Arg389 по сравнению с больными, гомозиготными по Gly389 аллелю. Получены данные, свидетельствующие о влиянии Ser49Gly и Arg389Arg генотипов β_1-АР на структуру левого желудочка у пациентов с тяжелой СН. Выявлено, что Arg389Arg тип полиморфизма гена β_1-АР ассоциируется с достоверным уменьшением конечнодиастолического и систолического размеров, индекса массы левого желудочка, увеличением фракции выброса левого желудочка по сравнению с гомозиготными носителями Gly389 аллеля.

Выводы. Таким образом, наличие Arg389 аллеля и Ser49Gly генотипа может оказывать влияние на кардиогемодинамические показатели у пациентов с тяжелой СН.

Ключевые слова: сердечная недостаточность, фармакогенетика, полиморфизм генов β_1-адренорецепторов, бета-адреноблокаторы, эхокардиографические показатели, артериальное давление.