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Effect of RAAS Genes Polymorphism for Recurrence of Paroxysmal Atrial Fibrillation Among Patients with Coronary Heart Disease Combined with Hypertension

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Abstract

The aim of the study was to detect the effect of RAAS genes polymorphism for recurrence of paroxysmal atrial fibrillation among patients with coronary heart disease combined hypertension.

Introduction

Atrial fibrillation (AF) is one of the most important medical and social problems of modern society, which is a common cause of ischemic stroke and leads to disability. The incidence of embolic complications is about 2.1% per year among the patients with paroxysmal AF, and is currently considered as a potentially dangerous arrhythmia with a significant increase in the incidence of serious complications [1].

Atrial fibrillation is a multifactorial disease. In its development such factors are leading, as old age, arterial hypertension, environmental factors, as well as genetic predisposition. The risk of development increases in those who have a history of at least one parent with this arrhythmia [2].

The onset of AF is accompanied by structural and electrophysiological remodeling of the atrial myocardium, which leads to left atrial (LA) dilatation. An increased size of the LA is considered as a predictor of arrhythmia recurrence.

The larger size LA has, the greater risk of AF recurrence patient has. It provides interesting information about the independent predictors of arrhythmia recurrence among patients with paroxysmal atrial fibrillation, which could predict such risk of left atrial dilatation [3].

The genetic predisposition of AF has a strong inherited component that is independent of concomitant cardiovascular disease. Up to a third of patients with this arrhythmia have common genetic variants that predispose to AF, although with a relatively low additional risk [4, 5].

The development of AF against the background of multifactorial diseases such as coronary heart disease (CHD) and hypertension can be promoted by gene polymorphisms. Currently, it is especially important to study the role of the genes of the renin-angiotensin-aldosterone system (RAAS), since recent data confirm that its activation plays an important role in maintaining AF among the patients with hypertension [6].

Such studies present the great practical interest for cardiologists, since the establishment of a relationship between genetic factors and RAAS mediators will allow to determine the risk of arrhythmia recurrence in a particular patient population. Therefore, in connection with the above, there is an interest to determine the relative risk of recurrence of paroxysmal atrial fibrillation among patients with coronary heart disease combined with hypertension, taking into account gene polymorphism, which determined the aim of this work.

The aim of the study was to detect the effect of RAAS genes polymorphism for recurrence of paroxysmal atrial fibrillation among patients with coronary heart disease combined hypertension.

Material and methods

To achieve this goal, a prospective study was conducted on the basis of the municipal non-profit enterprise "City Hospital № 10" of the Zaporizhzhia City Council. The sample of patients was conducted in the period from 2014 to 2019. The results of the study are based on data from a comprehensive examination and dynamic monitoring of 98 patients with paroxysmal AF on coronary heart disease with hypertension from Zaporozhzhia for the screening period, but during the observation period 6 patients refused to participate in research. The observation period was 6 months.

Criteria for inclusion in the study: male and female patients aged 45 to 70 years; recurrence of paroxysmal atrial fibrillation; verified stable coronary heart disease combined with stage II hypertension with known disease duration of more than 1 year; the patient's consent to participate in the study.

Criteria for exclusion from the study: atrioventricular block II-III degree; ventricular arrhythmias; circulatory failure more than II class of NYHA; oncological diseases; thyroid dysfunction; diabetes; hemodynamically significant heart defects; drug addiction, alcohol dependence, the presence of mental disorders; refusal of the patient from further observation.

The level of Aldosterone and Angiotensin-II in blood plasma was determined by ELISA method using standard kit “DBC Aldosterone ELISA” (DBC Inc., Canada) and “Human Angiotensin II ELISA” reagents made by Elabscience Biotechnology Inc. (USA) according to the method described in the application instruction for the test systems. The analysis was performed using "SUNRISE TS" (Austria) immunoassay analyzer.

Gene polymorphism was determined by polymerase chain reaction (PCR). Genomic DNA was isolated from peripheral blood leukocytes using a standard DNA-express blood test system (Litech, Russia) according to the manufacturer's instructions. Determination of SNP (Single Nucleotide Polymorphism) polymorphisms A1166C in the angiotensin II receptor type 1 gene (AGTR1) and T174M in angiotensinogen (AGT) was performed by real-time PCR using the amplifier "Rotor-Gene 6000", Australia. The structure of primers from standard sets "SNP-express-RV" (Litech) was used.

Statistical analysis

For dichotomous variables, multivariate analysis using stepwise binary logistic regression and ROC analysis (Receiver Operating Characteristic curve analysis) were performed. The cut-off point was found using the J-Youden index, calculating the area under the ROC curve (AUC - Area under the ROC curve) and its 95% CI, sensitivity (Se) and specificity (Sp). AUC, which value was greater than 0.5, was considered as statistically significant. Relative risk (RR) and its 95% confidence interval (CI) were calculated as the ratio of the incidence among patients exposed to the study factor to the incidence among patients not affected by the factor. The value of 95% CI BP, which did not exceed 1, was considered reliable. For statistical data processing the statistical software package PSPP (version 0.10.2, GNU Project 1998-2016, license GNU GPL) was used.

Results and Discussion

First, regression analysis was performed using two data sets: the first set combined patients who had recurrence of atrial fibrillation (n = 24), and the second - patients (n = 68) who did not have AF recurrence during the observation period. According to the results of a multivariate analysis of logistic regression, it was determined that aldosterone had P = 0.41, while angiotensin II had P = 0.01. For angiotensin II, ROC analysis was performed and it was statistically significant (AUC = 0.652, 95% CI 0.546 - 0.748), which at the cut-off point > 827.78 pg / ml, Sensitivity was 54.2% and Specificity = 75.0% often recurrent AF among patients with CHD in combination with hypertension.

Using the cut-off point for angiotensin II, the relative risk for recurrence of paroxysmal atrial fibrillation was determined. The results are shown in Table 1.

Table 1. The relative risk of occurrence for recurrence of paroxysmal atrial fibrillation

Variable	RR	95 % CI RR
Angiotensin II, >827,78 пг/мл	2.527	1.292 - 4.943
TT (n = 66) / TM+MM (n = 26)	1.523	0.763 - 3.039
AA (n = 55) / AC+CC (n = 37)	1.757	0.884 - 3.490
Angiotensin II & (TM+MM)	2.813	1.017 - 7.779
Angiotensin II & (AC+CC)	2.954	1.212 - 7.196

In the first data set, which combined patients with recurrence of arrhythmia from 24 people: there were 11 patients with Angiotensin II level lower than 827.78 pg / ml and 13 patients had level over 827.78 pg / ml, in another group of patients (n = 68), in which patients had no recurrence of AF during the follow-up period, apparently 51 individuals had Angiotensin II level lower than 827.78 pg / ml and 16 patients had level over 827.78 pg / ml. The relative risk was 2,527, 95% CI RR 1,292 - 4,943. For T174M polymorphisms in angiotensinogen (AGT) and A1166C in the angiotensin II receptor gene (AGTR1), the RR value was insignificant because 95% of CI RR crossed 1.

In a combined study of Angiotensin II with the genotype (TM + MM) of the T174M polymorphism in the first group (n = 9) patients with recurrence of arrhythmia, there were 5 people with Angiotensin II level more than 827.78 pg / ml, and in the second group (n = 9) there were 4 individuals, who had Angiotensin II level more than 827.78 pg / ml. The relative risk was 2.813, 95% CI RR 1.017 - 7.779 The combination of Angiotensin II with the genotype (AC + CC) of the A1166C polymorphism was among 13 patients in the group with recurrence of arrhythmia, in which the Angiotensin II level above 827.78 pg / ml had 8 individuals, while in the second group (n = 24) only 5 patients had an Angiotensin II level more than 827.78 pg / ml, and 19 individuals had the level of Angiotensin II was lower than 827.78 pg / ml. The relative risk was 2.954, 95% CI RR.

The results of our study showed the absence of an independent role for the polymorphisms of the RAAS T174M and A1166C genes in increasing the relative risk of recurrence of paroxysmal AF. This correlates with results from other studies that show that polymorphic markers give a low absolute, and more importantly indicate a possible stable phenotype. The association of AF cannot be easily revealed with a single locus, even with a large sample size. This is consistent with the complex nature of the disease, and clarifies the relatively minor role of gene polymorphism in cardiovascular disease. According to the results of the work, it was found that the polymorphism of the RAAS genes has a cumulative effect on the phenotype of the disease [6, 7].

Our results indicate that angiotensin II is involved in the mechanisms of AF recurrence. This is consistent with the data of experimental and clinical studies showing low potential proarrhythmogenic effects of angiotensin-II. Such as vasoconstriction, increased cardiac postload, and as it contributes to myocardial hypertrophy, which is also a proarrhythmogenic factor [8].

Thus, genetic testing is not currently used in routine clinical practice, but in the future, genomic analysis may provide an opportunity to improve the guidelines of the AF management. Genomics is becoming more common in cardiovascular medicine. The addition of complex analyzes of genomic and environmental risk to the examination guidelines of paroxysmal AF associated with CHD combined with hypertension will further improve individual approaches to the management of patients with this arrhythmia [9].

Conclusions

1. An independent predictor of arrhythmia recurrence was angiotensin II, whose level above 827.78 pg / ml increases the relative risk by 2.527 times.
2. Polymorphisms of the T174M and A1166C genes did not independently significantly increase the relative risk
3. Among the patients, who had the allelic gene M with genotypes (TM + MM) in combination with angiotensin II levels above 827.78 pg / ml the relative risk has increased in 2,813-fold of development the recurrence of arrhythmia.
4. Among the patients, who had allelic gene C with genotypes (AC + CC) in combination with angiotensin II levels above 827.78 pg / ml the relative risk has increased in 2,954-fold of development the recurrence of AF.

Conflicts of Interest: authors have no conflict of interest to declare.

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Ethical declaration. The study was approved by the local ethics committee of *State Institute «Zaporizhzhia Medical Academy of Postgraduate Education of Ministry of Health of Ukraine»*. The study was carried out in conformity with the Declaration of Helsinki.

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