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IMPACT OF ARTERIAL HYPERTENSION ON ATRIAL FIBRILLATION

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Abstract: Atrial fibrillation (AF) is the most prevalent arrhythmia in clinical practice. The most commonly encountered risk factor for AV development is arterial hypertension. The aim of the study is to evaluate the role of arterial hypertension on the clinical course of AF in patients with paroxysmal or persistent AF and restored sinus rhythm. Material and methods: Overall 101 patients – 51 females and 50 males at mean age 68,02 ± 7,001, with AF after sinus rhythm restoration were included in a clinical trial of one-year placebo-controlled treatment with spironolactone. They were analyzed for AF recurrence, hospitalization for AF, all-cause admissions, composite endpoint (recurrence episodes of AF, all-cause hospitalization and death) and value of biomarker of fibrosis Galectin-3 (Gal-3). Results: History for hypertension was documented in 86% of the participants. Patients with high blood pressure had significantly more recurrence episodes than normotensives, independently of the treatment on unifactorial and multifactorial analysis. Only the hypertension was predictive for recurrences with HR=2,86 (95% CI=1,01-8,07; p=0,047).There was a trend towards more hospitalizations for AF and all cause, but not significant. Hypertension was associated with doubled risk for composite end point, p=0,023.. Conclusion: Arterial hypertension is an important risk factor, which is very common and influences the clinical course of AF. It is associated with higher risk for recurrences and composite endpoint.
Keywords: atrial fibrillation, hypertension, Galectin-3

INTRODUCTION

Atrial fibrillation (AF) is the most prevalent arrhythmia in clinical practice. It affects 2% of the general population and varies with age and gender. AF is associated with increased morbidity and all-cause mortality [1-3]. A lot of risk factors contribute to the development and perpetuating of AF. The most commonly encountered of them is arterial hypertension [4-6]. Its prevalence in the general population is around 20-50% worldwide and among patients with AF it is 60-80% [7-9]. Hypertension leads to 1.8 fold increase of developing new-onset AF and 1.5-fold higher risk of progression to permanent AF [5,10]. Patients with high normal blood pressure were also found to be at increased risk for AF [11]. The exact pathways that lead to AF in patients with hypertension are not fully understood. Different hemodynamic and nonhemodynamic mechanisms are involved in the development of atrial cardiomyopathy - a complex of structural, contractile, architectural and electrophysiological alterations in the atria [12,13].Hypertension is associated with rise in left ventricular (LV) muscle mass, LV stiffness and LV diastolic dysfunction. These changes can cause elevated LA pressure, LA fibrosis and impaired emptying fraction. Hypertension is also one of the risk factors for thromboembolic events and bleeding in the patients with AF[14,15].The aim of the study is to evaluate the role of arterial hypertension for AF recurrence, hospitalization for AF, all-cause admissions, composite endpoint (recurrence episodes of AF, all-cause hospitalization and death) and value of biomarker of fibrosis Galectin-3 (Gal-3) in patients with paroxysmal or persistent AF and restored sinus rhythm.

MATERIALS AND METHODS

This is a substudy of a randomized single-center clinical observation of the effect of mineralcorticoidreceptror antagonist (MRA) Spironolactone on top of standard treatment in patients with atrial fibrillation after sinus rhythm restoration on the recurrence of the arrhythmia and on the changes in Gal-3 levels after 12 months. The patients were randomized into two groups. The active group received 25 mg Spironolactone on top of their usual therapy including antiarrhythmic medications which on week 2 or later may be up-titrated to 50 mg daily, and the control group was treated according to the 'usual care' following rhythm control. All participants were followed up for 1 year and had 5 follow-up visits – at 14 days, 1 month, 3 months, 6 months, 9 months, and, finally, at 12 months. At each visit the patient was examined, any recurrent episodes of AF and hospitalizations were documented. Standard 12-lead ECG was done at each visit. The diagnosis of AF was confirmed by ECG criteria and the sinus rhythm was restoredspontaneously or after medical or electrical cardioversion. The type of AF was classified according to the ESC Guidelines on AF 2010 and 2016 [2,16,17].

Inclusion criteria were as follows: age more than 55 years, restored sinus rhythm after an episode of paroxysmal/persistent AF, signed inform consent.Exclusion criteria included: history of, clinical and echocardiographic evidence of chronic heart failure NYHA class III-IV; open heart surgery during the last 3 months

for any indication; survivors of acute myocardial infarction and left ventricular dysfunction within 3 months of randomization; pregnancy; drug and alcohol abuse; presence of severe progressive concomitant disease with life expectancy less than 1 year; chronic kidney disease defined as serum creatinine more than 200 mmol/l or eGFR less than 40 ml/min/1.73 m2; liver cirrhosis Child C; treatment with powerful CYP3A4 inhibitors or inductors; serum potassium levels >5 mmol/l at screening; hypersensitivity towards MRA; metabolic acidosis; known thyroid pathology with lab results consistent with hyper- or hypothyroidism.At each visit, the patients were interviewed for episodes of recurrent arrhythmia, documented by their physicians or at the follow-up visits or incidental visits to the EDs. Information about their vital status or other hospitalizations was also collected personally or by their relatives in case of death. The etiology was considered to be due to CVD or other reasons by the investigators. Blood for galectin-3 determination was collected at baseline and one year after. Ten mL of blood was drawn from the antecubital vein of all patients into BD Vacutainer™ SST™ II Advance Tubes. The blood was allowed to clot for 30 min at room temperature and then centrifuged at 1,500×g for 15 min at 4°C. The separated serum was aliquoted into 1,5 mL polypropylene tubes, and stored at –80 °C until analysis. Samples with visible hemolysis were discarded from analysis.Serum galectin-3 levels were determined using enzyme-linked immunosorbent assay kit for quantitative measurement Galectin-3 AssayTM, LOT G3P-014 (BG Medicine, Waltham, MA, USA) according to manufacturer's instructions and were measured on StatFax 3200 microplate reader (Awareness Technology, Inc., USA). Calculation of results was performed with MikroWin 2000 ver. 4.31 software (MikrotekLaborsysteme GmbH, Germany) and expressed in ng/mL units.Of the all 101 patients in the study, in 67 Gal-3 was measured at baseline and in 62 both at baseline and in one year. All continuous variables are presented as means ± standard deviation for relatively normally distributed and as median /interquartile range/ for these with deviation from normality. When approximately normal distribution is present, the independent variables are compared by Student's t-test or ANOVA test in repeated measures in one patient. The paired t-test or one-sample t-test are applied for the differences in variables between the end and first visits. In case of lack of normality, nonparametric tests are used like Mann-Whitney's test. Because of skewed to the right distribution of Gal-3 values, we made a log transformation to improve the non-normal distribution. For categorical variables, absolute values and percents are presented and the chi-square test or Kendall's τ-analysis are used to test the null hypothesis. When the expected cell numbers are smaller than 5, then the exact Fisher's test is applied. In some cases, the paired Wilcoxon or signed rank tests are used. P-value <0.05 is used for significance testing. Correlation analyses using the Pearson's or Spearman's method were performed to test the relation between different continuous or categorical variables. Whenever appropriate, linear regression analysis is done to test the linear relationship between continuous dependant variable and treatment group, adjusted for major co-variates. Linear regression analyses were separately performed, with log Gal-3 at baseline, at the end of the study and for the difference between the visits as the dependent variable. For each separate covariate, a unifactor linear regression model is applied. The significance level 0.05 for keeping in the model and 0.1 for removing a variable from the model is used. In case of significance, a multivariate linear regression models are applied, with age, gender BMI and baseline Gal-3 values as covariates to adjust for. All analyses are performed on SPSS® version 19 (SPSS, Texas, USA).The project was approved by the local Committee of Medical Ethics of the University Hospital "St. Marina" Varna and complied with the Declaration of Helsinki. Informed consent was obtained in all patients.

RESULTS

History for hypertension was documented in 86% of the participants. Patients with high blood pressure had significantly more recurrence episodes than normotensives, independently of the treatment (HR=3.19, 95%CI 1.15-8.83, p=0.025). The results were confirmed also with multifactorial Cox regression analysis, including age, sex and treatment with spironolactone. Only the hypertension was predictive for recurrences with HR=2,86 (95% CI=1,01-8,07; p=0,047).The risk for hospitalization for AF in our hypertensive patients was higher, but it was not significant (p=0,312). The same was valid for all cause hospitalizations - 34% vs 14% (p=0,15). Hospitalizations for CVD other than AF are noticed only in hypertensive patients (NS). Hypertension was associated with doubled risk for compositeend point, p=0,023. Cox regression model, including diabetes, sex, hypertension, age and treatment with spironolactone showed that only hypertension was predictive for composite end point, p=0,045, HR2,62, 95% CI 1,02 – 6,73. There was no significant difference in levels of Gal-3 at baseline between hypertensive and normotensive patients (16,92 ±5,52 vs16,39 ±12,74, p=0,91). The presence of hypertension has not influenced significantly the change in Gal-3 levels for one year, but in normotensive patients Gal-3 decreases with 1.63ng/ml and in hypertensive increases with 0.1, p=0,16. Interestingly treatment with spironolactone in normotensive patients reduces logGal-3 with -0.0872 at end of study and in hypertensive logGal-3 rises with 0.0779.We found different effect of adding spironolactone in hypertensive and normotensive patients. Linear regression analysis for interaction

of hypertension with treatment with spironolactone showed that in the presence of both there is a rise in Gal-3 with 1.22 units (β coefficient 0.202) and in hypertension without spironolactone treatment Gal-3 decreases after 6 months with 0.92 ng/ml (β coefficient -0.081, p=0,05 for interference after accounting the interaction of sex, age and baseline Gal-3).

Discussion: In the literature there are more data on the risk for new-onset AF in patients with hypertension. The results of some studies confirmed the predictive role of hypertension for AF recurrences. Ma et al found that the risk of AF recurrence is higher in hypertensive subjects as compared to normotensive subjects [18]. In Manitoba Studytherateofatrialfibrillationwas 1.42 timesincreasedinmenwith a historyofhypertension [19]. One systematic review on the role of hypertension as a predictor for AF recurrences post radiofrequencycatheterablation found that from 11 trials, only 2 showed independentassociationsof hypertension withmorefrequent AF recurrence [20].

The association between blood pressure levels and Galectin-3 is not clear [21]. Some studies show such independently relationship [22]. Another study of Seferovic et al in diabetic patients failed to find differences in the level of the biomarkers in hypertensive and normotensive patients [23]. The effect of treatment with mineral-corticoid receptor antagonists on the markers of fibrosis needs further investigation [24].

CONCLUSION

Arterial hypertension is an important risk factor, which is very common and influences the clinical course of AF. It is associated with higher risk for recurrences and composite endpoint. Additional study is needed to find the correlation between AF, hypertension and fibrosis. The management of hypertension may reduce the adverse events in patients with AF.

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