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ADMA, subclinical changes and atrial fibrillation in the general population☆,☆☆

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ABSTRACT

Background: Pathways of oxidative stress, nitric oxide bioavailability and L-arginine derivatives are hypothesized to be related to atrial fibrillation (AF). Circulating methylated L-arginine metabolites can be assessed in the general population and may show an association with AF.
Methods: We determined L-arginine and its metabolites asymmetric dimethylarginine (ADMA), L-N^{ω}-monomethylarginine (NMMA) and symmetric dimethylarginine (SDMA) in the population-based Gutenberg Health Study (n = 5000), mean age 55 ± 11 years, 51% men, in association with clinical variables of AF such as electrocardiographic and echocardiographic measures and manifest AF.
Results: Individuals with AF (N = 161), 71% men, were older, mean age 64.9 ± 8.3 years. In Bonferroni-corrected multivariable-adjusted regression analyses we observed moderate inverse associations for L-arginine, SDMA, and L-arginine/ADMA ratio with ventricular heart rate, and for L-arginine and L-arginine/ADMA ratio with QTc interval. L-arginine was correlated with QRS duration. In echocardiographic analyses, SDMA was related to left atrial diameter and deceleration time, ADMA and NMMA were correlated with left ventricular mass.
ADMA (odds ratio [OR] 1.21, 95% confidence interval [CI] 1.11-1-32; p = 0.013) and NMMA (OR 1.17, 95% CI 1.09–1.26, p = 0.014) were related to prevalent AF. L-arginine/ADMA ratio was inversely associated (OR 0.8, 95% CI 0.71–0.90, p = 0.0082). Results were similar after adjustment for creatinine.
Conclusions: In our large, population-based cohort, we observed moderate associations of L-arginine metabolites and intermediate electrocardiographic and echocardiographic variables and AF. Our findings support further investigations to define the role of L-arginine derivatives in AF and their clinical utility.

1. Introduction

The pathophysiological background of common atrial fibrillation (AF) is not well established despite its increasing prevalence in the general population and significant public health burden [1,2]. Local and systemic signs of oxidative stress are pertinent to AF [3,4]. Myofibrillar energetics and function may be impaired, e.g., cardiac creatine kinase is redox sensitive and its oxidative damage contributes to atrial contractile dysfunction. High oxidative burden induces redox-responsive signaling pathways including NF-κB that lead to atrial and ventricular remodeling [5]. Two enzymes central to nitric oxide (NO) bioavailability

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are myocardial nicotinamide adenine dinucleotide phosphate oxidase and the endothelial nitric oxide synthase (eNOS). NO is produced from its precursor L-arginine. The dysfunction of the two enzymes with uncoupling of eNOS is responsible for the generation of reactive oxygen species in atria of patients with AF [6]. The L-arginine derivatives asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA) and L-N^{ω}-monomethylarginine (NMMA) are endogenous compounds of protein metabolism. ADMA is elevated as a result of oxidative protein damage of ADMA degrading enzymes and competitively inhibits NO synthesis with diverse detrimental effects on vasculature and organ function. Oxidative stress increases the activity of arginine methylating enzymes resulting in increased ADMA concentrations. ADMA perpetuates eNOS uncoupling [7]. Moreover, in healthy humans ADMA induces an elevation in blood pressure and arterial stiffness which both lead to an increased afterload and, secondarily, to left ventricular hypertrophy [8,9]. These vascular and arterial changes are known to be associated with AF [10,11]. Methylated L-arginine metabolites have been related to echocardiographic parameters in patients with chronic systolic heart failure and ADMA predicts outcome in dilated cardiomyopathy conditions that predispose to AF [12–14]. In small studies it could be demonstrated that ADMA plasma concentrations are elevated in individuals with AF and may be associated with adverse outcome [15,16]. In this context, we hypothesized that L-arginine derivatives are related to AF in the general population. To better understand the relation of L-arginine derivatives to AF, we further investigated their association with clinical variables, i.e., electrocardiographic and modern echocardiographic variables in a large, contemporary cohort.

2. Materials and methods

2.1. Study participants

The current data of this study are based on the first 5000 individuals enrolled in the Gutenberg Health Study. The cohort consists of a randomly selected population-based sample of European descent incepted in 2007 at the Department of Medicine 2, University Medical Center Mainz. Study participants are enrolled within 10-year age strata from 35–74 years. In clinical examination information on cardiovascular risk factors were collected based on a computer-assisted standardized interview. Anthropometric measures and non-invasive cardiovascular function testing were performed. Smoking status was categorized into the subgroups of non-smokers (never smokers and former smokers) and current smokers. Diabetes was diagnosed if the participant reported a physician diagnosis of diabetes and/or a fasting blood glucose concentration of ≥126 mg/dL (minimum 8-hour fast) or a blood glucose level of ≥200 mg/dL at any time was measured on site. Dyslipidemia was defined based on a physician's diagnosis and/or an LDL/HDL ratio of >3.5. Hypertension was defined by anti-hypertensive drug treatment and/or a mean systolic blood pressure of ≥140 mm Hg and/or a mean diastolic blood pressure of ≥90 mm Hg.

A history of cardiovascular disease implicated self-reported myocardial infarction, stroke, prevalent coronary heart disease and heart failure. Heart failure was determined by clinical aspects (New York Heart Association classification, heart failure medication) and echocardiographic examination (left ventricular ejection fraction < 55%).

A 12-lead electrocardiogram was registered of every study participant (GE Cardiosoft®). The QTc interval was automatically determined and corrected using the Bazett formula by the ECG machine. The diagnosis of AF was based on either reported AF in medical history and/or documentation of AF or atrial flutter on the study electrocardiogram [17]. AF was assessed by at least two physicians with cardiology training and experience in ECG reading. In difficult cases an electrophysiologist's opinion was consulted.

The study has been approved by the local Ethics Committee; prior to enrolment participants provided written, informed consent. All authors have read and approved the manuscript as written.

2.2. Biomarker determination

Creatinine was measured by routine laboratory method. L-arginine and arginine analogues were determined from fasting blood samples stored at −80 °C. L-arginine, SDMA, ADMA, and NMMA measurements were performed in plasma using liquid chromatography–tandem mass spectrometry as previously described in more detail [18].

2.3. Statistical methods

Data were analyzed for the total sample of 5000 individuals as well as for the subgroup of 161 individuals with AF. For two participants information on AF was missing leaving 4998 individuals for analysis. Available case analysis was used. Skewed variables including selected biomarkers were logarithmically transformed to achieve near normal distribution. In logistic regression models biomarkers were related to atrial fibrillation per one standard deviation increase. Models were adjusted for age and sex as well as for cardiovascular risk factors comprised in the Framingham risk score (age, sex, body mass index (BMI), systolic blood pressure, antihypertensive medication, diabetes, smoking, history of myocardial infarction, dyslipidemia and congestive heart failure) [19]. Further models additionally adjusted for creatinine were computed.

In multivariable regression analyses biomarkers were used as independent variables in relation to ECG and echocardiographic variables.

We further performed a net reclassification analysis on models based on clinical variables of the Framingham risk score and biomarkers associated with AF in multivariable-adjusted analyses to assess the additive discriminative ability of the biomarkers between individuals with AF and the rest of the sample for the biomarkers separately and in combination. Summary statistics of net reclassification improvement and integrated discrimination improvement were calculated.

$P < 0.05$ was used as a statistical significance threshold. A Bonferroni correction was performed for the number of tests applied in each analysis.

For all statistical analyses we applied R software, Version 3.1.2 (R Development Core Team, 2009, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org).

3. Results

3.1. Baseline data

Baseline characteristics for the total study cohort and by AF status are presented in Table 1. Out of 4998 individuals with a mean age of 55.5 ± 10.9 years, 50.8% men, 3.2% had AF.

About 3/4 in the group with AF were male. Individuals with AF were about 10 years older and had a higher BMI than those without AF. The cardiovascular risk factor burden in AF individuals was higher except for smoking. Heart failure was prevalent in 48.8% of AF participants with manifest AF. All L-arginine derivatives were differentially distributed in the study group. Higher concentrations were observed in participants with AF for ADMA, SDMA and NNMA, but lower concentrations for L-arginine and the L-arginine/ADMA ratio.

For clinical variables in the electrocardiogram and echocardiogram individuals with AF tended to have a higher ventricular rate, a longer QRS duration and QTc interval, as well as a larger left atrial diameter and higher left ventricular mass, as shown in Table 2. There were no clinically relevant differences in the left ventricular ejection fraction and variables representing diastolic function (E/A and deceleration time).