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Serum potassium levels and the risk of atrial fibrillation The Rotterdam Study

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ABSTRACT

Background: Atrial fibrillation is the most common sustained arrhythmia in the elderly. Serum potassium is associated with ventricular arrhythmias and cardiac arrest. Little is known about the association of serum potassium with atrial fibrillation. The objective of this study was to investigate the association of serum potassium and the risk of atrial fibrillation in a population based setting.
Methods: The study was performed within the prospective population-based Rotterdam Study. The study population consisted of 4059 participants without atrial fibrillation at baseline for whom baseline levels of serum potassium were measured. Atrial fibrillation was ascertained from centre visit ECG assessments as well as medical records.
Results: During a mean follow up of 11.8 years (SD = 5.2 yr), 474 participants developed atrial fibrillation. Participants with hypokalemia (<3.5 mmol/l) had a higher risk of atrial fibrillation (HR: 1.63, 95%CI: 1.03–2.56) than those with normokalemia (3.5–5.0 mmol/l). This association was independent of age, sex, serum magnesium, and other potential confounders. Especially in participants with a history of myocardial infarction, those with hypokalemia had a higher risk of atrial fibrillation than those with normokalemia (HR: 3.81, 95%-CI: 1.51–9.61).
Conclusions: In this study low serum levels of potassium were associated with a higher risk of atrial fibrillation.

1. Introduction

Atrial fibrillation is the most common sustained arrhythmia in the elderly. Atrial fibrillation is associated with a 3 to 5 times higher risk of stroke [1], and with a higher risk of heart failure, cardiac mortality, and total mortality [2,3]. Serum potassium, especially hypokalemia (<3.5 mmol/l), is suggested to be associated with a higher risk of cardiovascular disease, especially ventricular arrhythmias and cardiac arrest [4]. Few studies previously investigated the association of serum potassium with the risk of atrial fibrillation [5–8].Clinical studies showed that lower serum potassium levels were associated with a higher perioperative risk of atrial fibrillation [5,8]. However, studies on other populations did not show such an association [6,7]. One study in haemodialysis patients found low serum potassium to be associated with an increase in P-wave duration, a marker of atrial conduction [9]. P-wave duration increase has been associated with a higher risk of atrial fibrillation [10–14]. This supports the hypothesis that serum potassium is involved in atrial conduction, and possibly atrial fibrillation. However, as results from clinical studies may not be generalizable to the general population, results from a population-based cohort study with a large sample size are relevant.

Therefore, the objective of this study was to investigate the association of serum potassium with the risk of atrial fibrillation in a population-based setting of community-dwelling elderly.

2. Methods

2.1. Study population

The current study was performed within the Rotterdam Study, a population-based prospective cohort study, designed to examine the onset of, and risk factors for disease in older adults, which started with a baseline visit between 1990 and 1993 [15]. All participants aged 55 years and over in the Ommoord district of Rotterdam, The Netherlands, were invited (n = 10,275). Of them 7983 (78%) participated in the study. At baseline, participants were interviewed at home and were examined at the research center, which included a 10 s, 12-lead resting electrocardiogram (ECG). From that visit onward, participants were followed continuously and re-examined at three follow-up examination rounds (1993–1995, 1997–1999 and 2002–2004). In addition, information on the

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presence and occurrence of disease at baseline and during follow-up is available by collaboration with the general practitioners in the study area. General practitioners in The Netherlands have a central position in the Dutch health care system. They register all diagnoses available from their own work and the work from physicians in the hospital and the outpatient clinic. The medical ethics committee of the Erasmus Medical Center, Rotterdam, approved the study, and all participants gave informed consent. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Serum potassium assessment

At baseline of the study, blood samples were drawn by venapuncture from non-fasting participants and collected in 5-ml tubes containing 0.5 ml sodium citrate solution. All tubes were stored on ice before and after blood sampling. Serum potassium levels were measured within our clinical chemistry department using standard methods, expressed as mmol/l. Serum potassium was only assessed at baseline of the study, not during follow-up research center visits.

2.3. Assessment of atrial fibrillation

Prevalent and incident atrial fibrillation was ascertained using three methods [16]. We used ECGs that were obtained at baseline and during follow-up examinations. All ECGs were processed by the Modular ECG Analysis System (MEANS) which has a very high sensitivity and specificity for arrhythmias (96.6% and 99.5%, respectively) [17,18]. To verify the diagnosis of atrial fibrillation, all ECGs with a MEANS diagnosis of atrial fibrillation, atrial flutter, or any other rhythm disorder were recoded independently by 2 research physicians who were blinded to the MEANS diagnosis. The judgment of a cardiologist was taken as decisive in those cases in which disagreement persisted between the coding physicians. Additionally, all medical information of all study participants was obtained from general practitioners. In the Dutch health care system, patients have one general practitioner, who has a gatekeeper function, and this medical information therefore includes a registration and filing of medical information from their own work as well as the results from other physicians practicing in hospitals and outpatient clinics. Patients were only considered as a case of atrial fibrillation if the diagnosis by a medical specialist or by a general practitioner was ascertained with an ECG. Finally, information was obtained from a national registration of all hospital discharge diagnoses. Atrial fibrillation occurring during a serious disease resulting in death, during myocardial infarction or during cardiac operative procedures of patients who recovered during the hospital admission was not included as cases. We did not distinguish between atrial fibrillation and atrial flutter when we identified cases because both conditions are very similar with respect to risk factors and consequences [19,20].

2.4. Covariable assessment

Age at baseline and sex were included in all analyses. Body mass index (BMI) was calculated by dividing weight in kilograms by squared height in meters. Blood pressure was measured twice at the right upper arm with a random zero mercury sphygmomanometer in the sitting position. Systolic and diastolic blood pressure was calculated as the average of the two consecutive measurements. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol levels were measured with an automated enzymatic method. Data on medication use were obtained during the home interview by copying the labels of all the medication used. Information on smoking status was acquired from a questionnaire and distinguished into current, past, and never smokers. The glomerular filtration rate (GFR) was estimated by the abbreviated modification of diet in renal disease (MDRD) equation as recommended by the National Kidney Foundation [21,22]. A history of myocardial infarction was defined as a self-reported myocardial infarction that was confirmed by hospital admission or the presence of a myocardial infarction on the ECG [23]. Prevalent heart failure was assessed using a validated score based on the definition of heart failure by the European Society of Cardiology [24,25]. Prevalent diabetes mellitus was defined as the use of anti-diabetic medication or a pre- or post-load serum glucose level of >11.0 mmol/l. P-wave duration at baseline of the study was determined using MEANS, which determines common P-wave onsets and offsets for all 12 leads together on one representative averaged beat, with the use of thresholding techniques [18].

2.5. Vital status

Information on vital status was obtained on a weekly basis from the Central Register of Population of the municipality of Rotterdam, from collaborating general practitioners, and by collecting information during follow-up examination rounds. For the participants for whom information remained missing, the Central Registry of Genealogy of the Netherlands was consulted. This national institute receives population registry records of all inhabitants of the Netherlands who have died.

2.6. Population for analysis

Serum potassium levels were assessed at baseline in 5210 participants of the Rotterdam Study. Participants with prevalent atrial fibrillation at baseline ($n = 275$) or participants without a digitally stored ECG at baseline or with missing information on atrial fibrillation status were excluded ($n = 876$). This resulted in a study population of analysis of 4059 participants. All participants were followed from the baseline date of blood sampling until the date of incident atrial fibrillation, date of death, loss to follow up, or the end of follow up (January 1, 2008).

2.7. Statistical analysis

Baseline characteristics were obtained from all participants. Serum potassium levels were analyzed in several ways. First, serum potassium was analyzed as a continuous variable. Second, as the association of serum potassium with cardiovascular outcomes has previously been shown to be U-shaped [26], participants were categorized and the median category was used as a reference. Participants were categorized into commonly used clinically relevant categories of serum potassium: hypokalemia (<3.50 mmol/l), normokalemia (3.50–5.00 mmol/l), and hyperkalemia (>5.00 mmol/l). Furthermore, participants were also categorized into quintiles based on the levels of serum potassium. We used logistic and linear regression analyses to test whether the baseline characteristics were associated with serum potassium levels after adjustment for age and sex. Next, we assessed the association of the serum levels potassium with risk of incident atrial fibrillation, using Cox proportional hazards regression. First, we adjusted for age and sex. Second, we additionally adjusted for the following potential risk factors: systolic blood pressure, diastolic blood pressure, use of ACE-inhibitors, high-ceiling diuretics, low-ceiling diuretics, beta-blockers and other blood pressure lowering drugs, body mass index, total and HDL cholesterol, current smoking, past smoking, estimated glomerular filtration rate, history of myocardial infarction, presence of heart failure, presence of diabetes mellitus, P-wave duration, and serum magnesium levels. Finally, to test if the association was modified by the covariables in the model, interaction terms of the covariables*serum potassium were added separately. If this interaction term reached statistical significance (p-value < 0.05) we stratified the study population according to this covariable. All measures of association are presented with

Table 1
Baseline characteristics ($n = 4059$).

	Total sample ($n = 4059$)	Hypokalemia ($n = 108$)	Normokalemia ($n = 3933$)	Hyperkalemia ($n = 18$)
Age (years)	69.2(8.6)	70.9(8.6)	69.2(8.6)	77.7(8.7)*
Sex (female)	2425(59.7)	85(78.7)*	2394(60.9)	12(66.7)
SBP (mmHg)	139(22)	147(23)*	139(22)	141(34)
DBP (mmHg)	74(11)	78(12)*	73(11)	72(16)
Blood pressure lowering drugs:				
- ACE inhibitors	200(4.9)	5(4.6)	192(4.9)	3(16.7)*
- High ceiling diuretics	160(3.9)	7(6.5)	151(3.8)	2(11.1)
- Low ceiling diuretics	462(11.4)	61(56.5)*	399(10.1)	2(11.1)
- Beta-blockers	583(14.4)	25(23.1)*	553(14.1)	5(27.8)
- Other	135(3.3)	5 (4.6)	130(3.3)	0(0)
Body mass index (kg/m^2)	26.4(3.7)	26.7(3.8)	26.4(3.7)	26.0(3.5)
Total cholesterol (mmol/l)	6.7(1.2)	6.5(1.3)*	6.7(1.2)	6.9(1.3)
HDL cholesterol (mmol/l)	1.3(0.4)	1.4(0.4)	1.3(0.4)	1.1(0.3)*
Current smoker	979(24.1)	13(12.0)*	961(24.4)	5(27.8)
Past smoker	1634(40.3)	33(30.6)	1596(40.6)	5(27.8)
History of myocardial infarction	490(12.1)	14(13.0)	473(12.0)	3(16.7)
Presence of heart failure	97(2.4)	3(2.8)	91(2.3)	3(16.7)*
Presence of diabetes mellitus	415(10.2)	14(13.0)	395(10.0)	6(33.3)*
P-wave duration (ms)	119.6(13.5)	123.3(13.8)*	119.5(13.5)	122.7(15.6)
eGFR ($ml/min/1.73\ m^2$)	78.0(16.9)	75.8(15.6)	78.2(16.8)	53.4(21.2)*
Serum magnesium (mmol/l)	0.81(0.09)	0.78(0.08)	0.81(0.09)	0.84(0.09)*

Values are number of participants (%) or means (SD).
Abbreviations: ACE, Angiotensin converting enzyme; BMI, Body mass index; DBP, diastolic blood pressure; eGFR, estimated Glomerular Filtration Rate; HDL, high-density lipoprotein; SBP, systolic blood pressure.
* $p < 0.05$, compared to normokalemia, adjusted for age and sex.