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

Bouwe P. Krijthe [a,b], Jan Heeringa [a], Jan A. Kors [c], Albert Hofman [a,b], Oscar H. Franco [a], Jacqueline C.M. Witteman [a], Bruno H. Stricker [a,b,c,d,*]

[a] Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands
[b] Netherlands Consortium for Healthy Aging (NCHA), The Netherlands
[c] Department of Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands
[d] Inspectorate of Health Care, the Hague, The Netherlands

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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

* Corresponding author at: Department of Epidemiology, Erasmus Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands. Tel.: +31 10 7044294; fax: +31 10 7044657.
E-mail address: b.stricker@erasmusmc.nl (B.H. Stricker).

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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.

95% confidence intervals. Data were analysed using PASW SPSS statistical software, version 20.0 (IBM, Armonk, New York, USA).

3. Results

3.1. Baseline characteristics of the study population

Baseline characteristics are summarized in Table 1. The population for analysis consisted of 4059 participants. The mean age of the population at baseline was 69.2 years (SD = 8.6) and included 2425 (59.7%) females. During a mean follow-up of 11.8 years (SD = 5.2), 474 participants developed atrial fibrillation. The mean serum potassium level was 4.10 mmol/l (SD = 0.31), and ranged from 2.40 to 5.51 mmol/l. Compared to participants with normokalemia, those with hypokalemia were more likely to be female, to use low-ceiling diuretics or to use beta-blocking drugs, and were less likely to smoke. Also participants with hypokalemia had higher systolic and diastolic blood pressure, lower total cholesterol and had a longer P-wave duration after adjustment for age and sex.

3.2. The association of serum potassium levels with atrial fibrillation

Serum potassium levels were inversely associated with the risk of atrial fibrillation after adjustment for age and sex, but not in a multivariable adjusted model (HR per SD increment in serum potassium: 0.96, 95%-CI: 0.87–1.05) (Table 2). Participants with hypokalemia were at higher risk of atrial fibrillation than those with normal values after adjustment for age and sex (HR: 1.81, 95%CI: 1.17–2.81) (Table 2). Also in a multivariable adjusted model this association remained statistically significant (HR: 1.62, 95%-CI: 1.02–2.55). When analyzed in quintiles, the lowest quintile of serum potassium levels was associated with a higher risk of atrial fibrillation than the median (reference) quintile in a multivariable adjusted model (HR: 1.37, 95%-CI: 1.02–1.84) (Table 2). In the multivariable adjusted models, also P-wave duration was associated with the risk of atrial fibrillation (HR per SD increment in P-wave duration: 1.20, 95%-CI: 1.10–1.31).

Table 2
The association of serum potassium with risk of atrial fibrillation.

Serum potassium (mmol/l)	N	*n*(%)	Model 1[a] HR	95%-CI	Model 2[b] HR	95%-CI
Continuous, per SD	4059	474 (11.7)	0.91	(0.83–1.00)	0.96	(0.87–1.05)
Categories						
Hypokalemia (<3.50)	108	21 (19.4)	1.81	(1.17–2.81)	1.62	(1.02–2.55)
Normokalemia (3.50–5.00)	3933	451 (11.5)	1	(Ref.)	1	(Ref.)
Hyperkalemia (>5.00)	18	2 (11.1)	0.98	(0.24–3.95)	0.96	(0.24–3.91)
Quintiles						
Q1. (2.40–3.85)	820	122 (14.9)	1.61	(1.21–2.14)	1.37	(1.02–1.83)
Q2. (3.86–4.00)	826	79 (9.6)	0.97	(0.71–1.33)	0.95	(0.69–1.30)
Q3. (4.01–4.16)	779	77 (9.9)	1	(Ref.)	1	(Ref.)
Q4. (4.17–4.32)	831	92 (11.1)	1.11	(0.82–1.51)	1.12	(0.83–1.52)
Q5. (4.33–5.51)	803	104 (13.0)	1.27	(0.94–1.70)	1.24	(0.92–1.68)

Notes:
Abbreviations: HR; Hazard rate ratio, N; total number of participants, *n*; number of those that developed atrial fibrillation during follow up (% of N).
[a] Adjusted for age and sex.
[b] Adjusted for age, sex, systolic blood pressure, diastolic blood pressure, use of ACE inhibitors, low-ceiling diuretics, high ceiling diuretics, beta blockers and other blood pressure lowering drugs, body mass index, total and HDL cholesterol, current smoking, past smoking, history of myocardial infarction, presence of heart failure, presence of diabetes, estimated glomerular filtration rate, P-wave duration, serum magnesium.

3.3. Factors modifying the association of serum potassium levels with atrial fibrillation

The additional interaction terms of: use of high-ceiling diuretics* hypokalemia and a history of myocardial infarction*hypokalemia, in the multivariate model were statistically significant (*p*-value: 0.038 and 0.036 respectively). Subsequent stratified analyses showed that especially in participants with a history of myocardial infarction, participants with hypokalemia were associated with a higher risk of atrial fibrillation than participants with normokalemia (HR: 3.80, 95%-CI: 1.50–9.63) (Table 3).

4. Discussion

In this study, low levels of serum potassium were associated with a higher risk of atrial fibrillation. This association was independent of several potential confounders. We found that hypokalemia (<3.50 mmol/l) was associated with an increased risk of atrial fibrillation in comparison to normokalemia. Also participants in the lowest quintile of serum potassium (<3.85 mmol/l) were associated with a higher risk compared to the median quintile.

Several studies previously investigated the influence of potassium in the development of atrial fibrillation. Also in a study among 2402 patients undergoing cardiac surgery, preoperative hypokalemia (<3.5 mmol/l) was associated with atrial fibrillation compared to higher levels of atrial fibrillation [5]. A study of 253 patients undergoing

Table 3
The association of serum potassium with risk of atrial fibrillation, stratified analyses.

Serum potassium (mmol/l)	N	*n*(%)	Model 1[a] HR	95%-CI	Model 2[b] HR	95%-CI
Use of high ceiling diuretics						
No						
Hypokalemia (<3.50)	101	18 (17.8)	1.66	(1.03–2.66)	1.45	(0.88–2.36)
Normokalemia (3.50–5.00)	3782	429 (11.3)	1	(Ref.)	1	(Ref.)
Hyperkalemia (>5.00)	16	2 (12.5)	1.07	(0.27–4.32)	1.04	(0.26–4.23)
Yes						
Hypokalemia (<3.50)	7	3 (22.7)	3.90	(1.14–13.32)	2.44	(0.40–15.00)
Normokalemia (3.50–5.00)	151	22 (15.1)	1	(Ref.)	1	(Ref.)
Hyperkalemia (>5.00)	2	0 (0)	NA	(NA)	NA	(NA)
History of myocardial infarction						
No						
Hypokalemia (<3.50)	94	15 (16.0)	1.51	(0.90–2.54)	1.24	(0.73–2.13)
Normokalemia (3.50–5.00)	3460	375 (10.8)	1	(Ref.)	1	(Ref.)
Hyperkalemia (>5.00)	15	1 (6.7)	0.60	(0.08–4.28)	0.54	(0.07–3.84)
Yes						
Hypokalemia (<3.50)	14	6 (42.9)	3.36	(1.46–7.76)	3.80	(1.50–9.63)
Normokalemia (3.50–5.00)	473	76 (16.1)	1	(Ref.)	1	(Ref.)
Hyperkalemia (>5.00)	3	1 (33.3)	3.37	(0.46–24.58)	2.83	(0.33–24.54)

Notes:
Abbreviations: HR; Hazard rate ratio, N; total number of participants, *n*; number of those that developed atrial fibrillation during follow up (% of N).
[a] Adjusted for age and sex.
[b] Adjusted for age, sex, systolic blood pressure, diastolic blood pressure, use of ACE inhibitors, low-ceiling diuretics, high ceiling diuretics, beta blockers and other blood pressure lowering drugs, body mass index, total and HDL cholesterol, current smoking, past smoking, history of myocardial infarction, presence of heart failure, presence of diabetes, estimated glomerular filtration rate, P-wave duration, serum magnesium.

cardiac surgery, showed an association between lower serum potassium (<3.9 mmol/l) and an increased risk of atrial fibrillation during the postoperative period [8]. In one study in 517 patients with an acute myocardial infarction, hypokalemia was not associated with a higher risk of atrial fibrillation during hospitalization compared to normokalemia [6], but these differences in results may be caused by a lack of power or by differences in populations as patients with an acute myocardial infarction may not be comparable to the general population or to a population undergoing cardiac surgery. In addition we found that especially in participants with a history of myocardial infarction, low serum potassium was associated with a higher risk of atrial fibrillation. Although these subgroup analyses were based on small numbers, this is further supported by other studies that suggest that especially cardiovascular patients are prone to develop ventricular arrhythmias or sudden cardiac death in case of low serum potassium [4]. Finally, we found that the association of low serum potassium with the risk of atrial fibrillation might be modified by the use of high-ceiling diuretics. High-ceiling diuretics can cause hypokalemia, thereby they might amplify the risk of atrial fibrillation in participants that are at lower levels of serum potassium. However the mechanisms behind these observed interactions have not been completely elucidated.

We also found that low serum potassium is associated with an increase in P-wave duration, a marker of atrial conduction time, in our study population. This has also been shown in a study in haemodialysis patients [9]. P-wave duration increase is associated with a higher risk of atrial fibrillation [10–14]. Although in our data prolonged P-wave duration was associated with a higher risk of atrial fibrillation, this can not solely explain how low serum potassium leads to an increased risk of atrial fibrillation as both P-wave duration and low serum potassium levels were independently associated with the risk of atrial fibrillation when added simultaneously in one model.

The most likely mechanism through which serum potassium leads to an increased risk of atrial fibrillation is by the influence of potassium on the cell membrane potential. It is proposed that a low serum potassium level causes cellular hyperpolarity, increases resting potential and hastens depolarization [27]. However, no conclusions on causality can be drawn from our results. It can not be excluded that a low serum potassium level is a marker of underlying conditions which predispose to atrial fibrillation.

4.1. Strengths and limitations

Strengths of this study are its population-based design, with follow-up up to 18 years. This study included extensive information on clinical details and multiple covariables. The study is limited in that we were not able to distinguish between paroxysmal and persistent atrial fibrillation. Also as atrial fibrillation may occur without symptoms, false-negative misclassification may have occurred. However we used three different methods for the case gathering and assessment, and included every clinically recognized case from two different sources of medical records. In addition, we included repeated screening ECG assessments of the study population at the research centre. Moreover, any false-negative misclassification is likely to be random and therefore will have led to an underestimation of the true risk estimate. Our study is limited to one baseline assessment of serum potassium. Also our stratified analyses were based on small numbers and results should therefore be interpreted cautiously.

4.2. Conclusions

This study with extensive follow-up showed that low serum potassium levels are associated with higher risk of atrial fibrillation. These results were obtained in the general population, and were independent of several potential confounders. The proportion of cases due to low serum potassium may be low but as serum potassium is easily and frequently obtained this finding is still relevant at a population level, also because atrial fibrillation is relatively common and may have serious consequences such as stroke. Further studies with repeatedly measured serum potassium and the risk of atrial fibrillation would be interesting.

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Conflict of interest

The authors declare that there are no financial competing interests associated with this study.

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