

Serum Potassium Levels Inversely Correlate with D-Dimer In Patients with Acute-Onset Atrial Fibrillation

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Abstract

Background: D-dimer values are frequently increased in patients with atrial fibrillation (AF) compared to subjects in sinus rhythm. Hypokalemia plays a role in several cardiovascular diseases, but little is known about the association with AF.

Objective: D-dimer values are frequently increased in patients with atrial fibrillation (AF) compared with subjects in sinus rhythm. Hypokalemia plays a role in several cardiovascular diseases, but little is known about the association with AF. The aim of this study was to investigate correlations between D-dimer and serum potassium in acute-onset AF (AAF).

Methods: To investigate the potential correlation between the values of serum potassium and D-dimer in patients with AAF, we retrospectively reviewed clinical and laboratory data of all emergency department visits for AAF in 2013.

Results: Among 271 consecutive AAF patients with D-dimer assessments, those with hypokalemia ($n = 98$) had significantly higher D-dimer values than normokalemic patients (139 versus 114 ng/mL, $p = 0.004$). The rate of patients with D-dimer values exceeding the diagnostic cut-off was higher in the group of patients with hypokalemia than in those with normal serum potassium (26.5% versus 16.2%; $p = 0.029$). An inverse and highly significant correlation was found between serum potassium and D-dimer ($r = -0.21$; $p < 0.001$), even after adjustments for age and sex (beta coefficient -94.8 ; $p = 0.001$). The relative risk for a positive D-dimer value attributed to hypokalemia was 1.64 (95% CI, 1.02 to 2.63; $p = 0.040$). The correlation remained statistically significant in patients free from antihypertensive drugs ($r = -0.25$; $p = 0.018$), but not in those taking angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, or diuretics.

Conclusions: The inverse correlation between values of potassium and D-dimer in patients with AAF provides important and complementary information about the thromboembolic risk of these patients. (Arq Bras Cardiol. 2015; 104(3):181-184)

Keywords: Atrial Fibrillation; Hypokalemia; Fibrinogen / metabolism; Tromboembolism; Potassium.

Introduction

It is well established that atrial fibrillation (AF) carries a significant risk of mortality and morbidity in the general population, and the high propensity of clotting in the left atrial appendage represents the leading clinical concern for these patients¹. Hence, it was recently emphasized that the presence of AF increases the risk of cerebrovascular accidents by 2.6-fold to 4.5-fold throughout all classes of age².

The association between AF and hypercoagulability has been recognized for a long while³, but only recently have scientists focused on biomarkers associated with thromboembolism in patients with AF. D-dimer, a circulating biomarker of both thrombogenesis and thrombus turnover, is considered the gold standard in this field⁴. Several studies showed that D-dimer levels are higher in AF patients

compared with matched controls in sinus rhythm⁵⁻⁷ and that patients with paroxysmal AF have intermediate levels of D-dimer compared with patients with chronic AF and controls in sinus rhythm, correlating with intermediate risk of thromboembolism⁵. In a previous study⁸, it was demonstrated that AF represents one of the leading causes of D-dimer elevation in a large number of patients seeking emergency department (ED) treatment for suspected venous thromboembolism.

Although it is generally acknowledged that hypokalemia represents a common and reversible factor in the natural history of cardiovascular disease, little information is available about the association between serum potassium concentration and atrial arrhythmias⁹. Myocardocyte repolarization depends on potassium influx, and hypokalemia lengthens the action potential and increases QT dispersion, thus reflecting electrical dishomogeneity^{10,11}. Pre-treatment with intravenous magnesium and potassium solution is effective in lowering energy levels in external electrical cardioversion for persistent AF^{12,13}. Only recently the association between serum potassium levels and the incidence of AF has been demonstrated in a group of Danish patients¹⁴, despite the elusive underlining mechanisms. Therefore, a retrospective investigation was performed to

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Manuscript received August 4, 2014; revised manuscript October 6, 2014; accepted October 6, 2014.

DOI: 10.5935/abc.20140187

assess the potential correlation between serum potassium and D-dimer levels in patients with acute-onset atrial fibrillation (AAF).

Methods

This study included all episodes of AAF recorded in a large urban ED (90.000 visits per year, serving an area with a population of approximately 435.000) in 2013, which were retrospectively reviewed from the hospital's electronic database. The analysis was limited to cases with onset of AF recorded within 48 hours from an ED visit and for whom D-dimer assessment was requested by an emergency physician in order to exclude an underlying cause of AAF (namely a pulmonary embolus, based mainly on a Gestalt perception). Only in a minority of instances was this the case.

According to currently available guidelines, the definition of AAF included both first-diagnosed AF and paroxysmal AF (PAF)¹.

In all patients, the concentration of D-dimer was measured using HemosIL D-dimer HS for ACL TOP (Instrumentation Laboratory, Bedford, MA), a latex-enhanced turbidimetric immunoassay characterized by a total imprecision lower than 6.6%, a detection limit of 21 ng/mL, and a diagnostic cut-off of 243 ng/mL. Serum potassium was assessed with indirect ion selective electrode (ISE), on a Beckman Coulter AU 5800 (Beckman Coulter Inc., Brea CA, USA). According to a local and validated practice, hemolyzed specimens displaying a concentration of cell-free hemoglobin > 0.5 g/L are systematically rejected, so spurious hyperkaliemic samples were not included in this study. The quality of laboratory data was validated throughout the study period by regular internal quality control (IQC) procedures and participation in an External Quality Assessment Scheme (EQAS).

Results of testing were finally expressed as median and interquartile range (IQR). The significance of differences was evaluated by the Mann-Whitney-Wilcoxon Test (for continuous variables) and the chi-squared test with Yates's correction for continuity (for categorical variables), using Analyse-it (Analyse-it Software, Ltd, Leeds, UK). Simple linear and multivariate regression analyses were also used to identify factors potentially associated with D-dimer values (included as a continuous variable). The Relative Risk (RR) was calculated using MedCalc Version 12.3.0 (MedCalc

Software, Mariakerke, Belgium). The investigation was performed in accordance with the Declaration of Helsinki and under the terms of all relevant local legislation.

Results

Overall, 474 cases of AAF were recorded in the ED in 2013, 271 (134 males and 137 females; mean age 67 ± 12 years) with a D-dimer measurement available upon admission. The 98 patients with hypokalemia (i.e., serum potassium levels <4.0 mmol/L) had significantly higher D-dimer values than those with serum potassium ≥ 4.0 mmol/L (139 ng/mL, IQR 70-270 ng/mL versus 114 ng/mL, IQR 58-195 ng/mL; $p = 0.004$) (Table 1). The percentage of patients with D-dimer values exceeding the diagnostic cut-off of the method (i.e., 243 ng/mL) was also significantly higher in the group of AAF patients with hypokalemia (26/98; 26.5%) than in those with serum potassium ≥ 4.0 mmol/L (28/173; 16.2%; $p = 0.029$). An inverse and highly significant correlation was found between serum potassium and D-dimer values ($r = -0.21$; $p < 0.001$), which remained statistically significant after adjustment for age and sex (beta coefficient -94.8; $p = 0.001$). The RR for positive D-dimer attributable to hypokalemia was 1.64 (95% CI, 1.02 to 2.63; $p = 0.040$).

The patients were subsequently classified according to the pharmacologic treatment used at the time of ED presentation. A total of 147 patients were free from antihypertensive drugs, whereas 60 were taking angiotensin receptor blockers (ARBs), 54 were taking angiotensin-converting enzyme inhibitors (ACE-Is), and 54 were taking diuretics (37 took thiazides, 14 took loop diuretics, 9 took spironolactone; and 6 patients took an association of thiazide and spironolactone). Forty-one patients were administered double therapy and 3 patients triple therapy. Interestingly, the correlation between serum potassium and D-dimer values remained statistically significant in patients free from antihypertensive drugs ($r = -0.25$; $p = 0.018$), but not in those taking ARBs ($r = -0.06$; $p = 0.76$), ACE-Is ($r = -0.16$; $p = 0.39$) or diuretics ($r = -0.17$; $p = 0.21$).

Discussion

Humans have lived for millennia eating a potassium-rich, sodium-poor diet (i.e., a potassium-to-sodium intake

Table 1 – Demographical and laboratory data (median and interquartile range) of the study population

	Serum potassium		p
	< 4 mmol/L	≥ 4 mmol/L	
N	98	173	
Age (years)	69 (58-76)	68 (58-75)	0.35
Sex (M/F)	43/55	91/82	0.21
D-dimer			
- Value (ng/mL)	139 (77-270)	114 (58-195)	0.004
- Value > cut-off	26/98	28/173	0.029

ratio ranging from 3 to 10), so that biological systems have developed in a “sodium-retaining and potassium-wasting” environment^{15,16}. The human genetic code has also evolved accordingly, and the cardio-reno-vascular system has undergone a gradual adaptation for successful living in these ancestral conditions. The remarkable changes that have occurred in dietary habits throughout past centuries are mostly characterized by a shift towards a sodium-rich diet (i.e., a potassium-to-sodium intake ratio usually < 0.4), and have also been associated with a marked trend towards sodium overload and potassium depletion¹⁷ with significant adverse cardiovascular effects¹⁸.

The risk of developing AF constantly increases with age, and is mostly associated with hypertension in Western countries¹⁹. Although the risk of AF has also been associated with a variety of genetic²⁰, infectious (i.e., namely rheumatic heart disease)²¹, and environmental²² factors, no information is available regarding the potential association between serum potassium concentration, the risk of developing AF, or the thromboembolic tendency in patients with established AF.

Recent evidence from hypertension and heart failure clinical trials show that drugs acting on the renin-angiotensin system (i.e., angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) are effective in the primary prevention of AF, although this benefit seems to be limited to patients with systolic left ventricular dysfunction or left ventricular hypertrophy, and is not clearly related to their potassium-sparing effect²².

The results of this retrospective analysis of 271 cases of AAF demonstrate for the first time that a significant negative correlation exists between values of serum potassium and D-dimer, which is a well-established biomarker of thrombosis and fibrinolysis⁴. This finding may have significant clinical implications. Due to a substantially increased risk of cardiovascular mortality and morbidity, AF requires early and appropriate management. Specifically, AAF is a frequent reason for ED evaluation so that the appropriate management strategy should encompass accurate risk assessment of stroke, bleeding, and cardiovascular morbidity. Along with conventional risk assessment tools such as CHA₂DS₂-VASc and HAS-BLED scores, and troponin¹, D-dimer and potassium levels may hence provide important complementary information about the thromboembolic risk and prognosis of these patients, especially in those free from antihypertensive drugs. It is also noteworthy that the greater risk of hypercoagulability that we

have observed in AAF patients with hypokalemia, as mirrored by the remarkably higher rate of increased D-dimer values, may provide a reliable foundation for planning interventional trials aimed at establishing whether correction of hypokalemia, or even the modest elevation of serum potassium value within the physiological range, may be effective in lowering the risk of thromboembolic complications in these patients. This is also supported by experimental data suggesting that an increase of potassium concentration in blood is associated with a number of antithrombotic effects such as inhibition of free radical generation, reduction of platelet hyperaggregability and an overall decrease of the endogenous prothrombotic potential²³.

Potential limitations of the study are represented by the retrospective nature of it, and its monocentric design.

Conclusions

The inverse correlation between values of potassium and D-dimer in patients with AAF may provide, when added to conventional risk assessment tools such as CHA₂DS₂-VASc and HAS-BLED scores, and troponin, important and complementary information about the thromboembolic risk and the prognosis of these patients, especially in those free from antihypertensive drugs.

Author contributions

Conception and design of the research: Cervellin G, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Cervellin G, Picanza A, Lippi G; Statistical analysis: Bonfanti L, Picanza A.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

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