DOI: http://dx.doi.org/10.25239/SHJ/Vol6/No3/Article

Original Article

Potassium Abnormalities In Cardiac Patients Taking Angiotensin-converting enzyme inhibitors, Angiotensin II Receptor Blockers and Diuretics

Author(s): Faisal AE Suliman^, Nagla FA Haggar*, Abduelbagi DA Eltayb*, Shaza AS Abdoalraheem**

*Ahmed Gasim Cardiac Surgery & Renal Transplant Centre, Khartoum, Sudan
^Corresponding Author, faisalaes@yahoo.com

Abstract

Background:
Potassium is an essential mineral for cardiac function. It is mostly an intracellular element. Concomitant diseases, medications, and diet can affect potassium level.
Objective:
To determine the frequency of abnormalities in serum potassium level in cardiac patients taking Angiotensin-Converting Enzyme Inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and diuretics on a regular Sudanese diet.
Methods:
A descriptive prospective Hospital-based study was conducted in Ahmed Gasim Cardiac Surgery & Renal Transplant Centre. Participants were cardiac patients taking ACEIs, ARBs, and diuretics. Data was collected by using a structured questionnaire and analyzed by computer software Statistical package for the social sciences program (SPSS version 18.0).
Results:
The study was conducted in 120 patients. Males were 67 (55.8%), and females were 53 (44.2%). 98 (81.7%) patients were ≥ 50years old. Patients with Ejection Fraction < 50% were 74 (61.7%). Abnormal serum creatinine was found in 31 (25.8%) patients. 90(75%) patients were taking furosemide, 77(64.2%) were taking spironolactone, 81(68%) were taking ACEIs, and 29 (24.2%) patients were taking ARBs.
Discussion & Conclusion:
Serum potassium changes are not common among cardiac patients taking ACEIs, ARBs, and diuretics on a regular Sudanese diet. Hyperkalaemia due to ACEIs was only seen in patients with abnormal renal function and was not seen with ARBs. Regular follow-up of serum potassium is essential in patients with abnormal renal function taking these medications.
Keywords
Potassium, renal function, heart failure, ACEI, ARB, diuretic, Sudanese Diet Hyperkalaemia, hypokalaemia.

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Introduction:

Potassium is an essential mineral for the function of all cells; the daily requirement of potassium is 2.5 to 5.5 g/day. Most of the potassium is intracellular, only 5% is extracellular, however changes in whole body potassium are reflected in the serum potassium (1). Potassium homeostasis has a critical physiological role in the normal function of the cardiovascular system. There are multiple possible mechanisms through which it achieves this action: e.g. increased serum potassium inhibits free radical formation from vascular endothelium and macrophages, inhibits platelet aggregation and arterial thrombus formation (2). Epidemiological and clinical studies showed that a high potassium diet lowers individual and average population blood pressure (3). Increased potassium intake reduces cardiovascular mortality and renal disease progression (1).

On the other hand, reduced serum potassium is associated with worse outcomes, such as lethal ventricular arrhythmias in patients with acute myocardial infarction (4) , Heart Failure (HF) and left ventricular hypertrophy (1, 5). The kidneys play a crucial role in maintaining potassium homeostasis, and the reduction of renal function with aging is responsible for frequent hyperkalemia in the elderly (6, 7). In patients with HF risks for both hypokalaemia and hyperkalemia are present. Hypokalaemia is more common in the early stages of HF when renal function is better preserved. On the other hand, the risk of hyperkalemia increases with progressive HF & worsening of renal function. Most of the HF medications influence serum potassium homeostasis. Loop diuretics cause hypokalaemia, which may require physicians to give potassium supplementation; sometimes in conjunction with potassium-sparing diuretics. Beta-blockers increase intracellular potassium shift leading to hypokalaemia. Angiotensin Converting Enzyme Inhibitors (ACEIs) and to a lesser extent, Angiotensin Receptor Blockers (ARBs) cause hyperkalemia by decreasing the glomerular filtration rate (GFR) and aldosterone levels. Spironolactone reduces aldosterone level and increases the frequency of hyperkalemia(8).

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Methods:

Objective: To determine the frequency of abnormalities in serum potassium level in cardiac patients taking ACEIs, ARBs and diuretics on a regular Sudanese diet.

This is a descriptive prospective hospital-based study conducted at Ahmed Gasim Cardiac Surgery and Renal Transplant Centre in the period from September 2013 to April 2014. The study population was Sudanese patients age 18 and above, with cardiac diseases, admitted to the cardiac ward &/or attending the outpatient clinics.

Inclusion Criteria: Patients with hypertension and HF taking ACEI, ARB, and diuretics (spironolactone or furosemide).

Exclusion Criteria: Patients with causes which are known to affect serum potassium level, e.g., acute/or chronic diarrhea, burn, rhabdomyolysis, etc.

Data Collection: During a direct interview, a structured questionnaire was completed and updated through three subsequent visits. Demographic (age, gender) and clinical data (type of cardiac disease) was collected. Echocardiographic left ventricular systolic function (according to Ejection Fraction – EF) and medication taken by the patients ACEIs, ARBs, diuretics, and potassium supplements were recorded. The patient's daily dietary potassium was assessed by the hospital dietician and recorded. Laboratory investigations including blood urea, serum creatinine, and serum potassium were also recorded. Hypokalaemia and Hyperkalaemia were defined as serum potassium less than 3.5 mEq/L and more than 5.5 mEq/L respectively.

Data Analysis: The data was analyzed using the statistical package for Social Science system (SPSS version18.0). The two-tailed significance level was set at a P-value of less than 0.05.

Ethical considerations: Ethical approval from the ethical review committee of the Sudan Medical Specialization Board in Khartoum was obtained. Signed informed consent was obtained from all surveyed participants. Participation in the survey was voluntary.

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Results:

Baseline Characteristics

- 120 patients were included in the study.
- Gender
  - Males were 67 (55.8%), and females were 53 (44.2%).
- Age
  - 98 (81.7%) patients were ≥ 50 years old.
  - 22 (18.3%) were <50 years old.
- EF
  - Patients with EF% < 50% were 74 (61.7%).
- Serum Creatinine was abnormal (>1.2 mg/l) in 31 (25.8%) patients.
- Medications:
  - 90 (75%) patients were taking furosemide.
  - 77 (64.2%) patients were taking spironolactone.
  - 81 (68%) patients were taking ACEIs.
  - 29 (24.2%) patients were taking ARBs.
- Potassium Level
  - 94 (78.3%) patients were normokalaemic.
  - 23 (19.2%) were hypokalaemic.
  - 3 (2.5%) were hyperkalaemic.

Findings: **(Table 1)**

- According to Age
  - In the age group ≥ 51 years
    - 15 (15.3%) patients were hypokalaemic.
    - 3 (3.1%) patients were hypokalaemic.
  - In the age group ≤ 50 years,
    - 8 (36.4%) patients were hypokalaemic.
    - None were hyperkalemic.
  - P-value=0.02

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- According to EF
    - In patients with EF% < 50%
        - 16 (21.6%) were hypokalaemic.
        - 3 (4.1%) were hyperkalaemic.
    - In patients with EF% > =50%
        - 7 (15.2%) patients were hypokalaemic.
        - None (0%) patient were hyperkalemic.
        - P-value= 0.048
- According to Creatinine
    - In patients with abnormal serum creatinine
        - 5 (16.1%) were hypokalaemic.
        - 3(9.8%) were hyperkalemic.
    - In patients with normal serum creatinine
        - 18 (22.2%) were hypokalaemic.
        - None were hyperkalemic.
        - P-value = 0.00003
- According to medication prescribed
    - Patients on ACEIs (81 or 67.5%)
        - 25(30.9%) had abnormal serum creatinine
            - 4 (16%) were hypokalaemic.
            - 2 (8%) were hyperkalaemic.
            - P-value = 0.046
        - 56 (69%) had normal serum creatinine
            - 12 (21.4%) were hypokalemic.
            - None were hyperkalemic.
            - P-value= 0.27
    - Patients on ARBs (29 or 24.1%)
        - 4(13.8%) had abnormal serum creatinine
            - 1 (25%) was hypokalaemic.
            - None were hyperkalemic.
            - P-value=0.16

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- 25 (86.2%) had normal serum creatinine
  - 6 (24%) were hypokalemic.
  - None were hyperkalemic.
  - P-value= 0.49

- Patients on furosemide (90 or 75%)
  - 27 (30%) had abnormal serum creatinine
    - 5(18.5%) were hypokalaemic.
    - 1(3.7%) was hyperkalemic.
    - P-value=0.009
  - 63 (70%) had normal creatinine
    - 14 (22.2%) were hypokalaemic.
    - None were hyperkalemic.
    - P-value=0.68

- Patients on spironolactone (77 or 64.1%)
  - 24 (31.2%) had abnormal serum creatinine.
    - 5(20.8%) were hypokalaemic.
    - None were hyperkalemic.
    - P-value= 0.009
  - 53 (68.8%) had normal creatinine
    - 13 (24.5%) were hypokalaemic.
    - None were hyperkalemic.
    - P-value=0.54

Discussion:

Our study shows that ACEIs, ARBs, and Furosemide were associated with changes in potassium homeostasis only in the presence of renal impairment; this has been demonstrated in other studies (7). Weir et al demonstrated that patients with conditions that reduce potassium excretion such as Chronic Kidney Disease, Diabetes, Or HF (HF), are at higher risk of serum potassium elevations. However, the risk is ≤ 2% in patients with normal renal function (9). Wilcox et al demonstrated that potassium depletion during furosemide administration to healthy subjects on a regular salt diet is prevented by normal renal function (10). However, in cardiac patients, the stimulation of

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renin, angiotensin, aldosterone system (RAAS) results in high levels of Renin, Aldosterone, and Angiotensin. There is also an increase in antidiuretic hormone (ADH) which is expected to result in hypokalaemia.

Furosemide-induced potassium losses are expected, provided that distal sodium (Na^+) delivery is not jeopardized (10). Hypokalaemia was seen in 21.1% of those tested and taking furosemide, which is comparable to Kjeldsen's review estimating (7-40%) hypokalaemia frequency in cardiac patients taking non-potassium sparing diuretics(11) . However, only in the presence of impaired renal function did furosemide administration showed a significant effect on serum potassium, possibly due to the high average potassium in the diet (8, 10).

Spironolactone in patients with normal renal function did not affect serum potassium changes. Studies have shown that gender may play a role in serum potassium changes with spironolactone; with females more prone to hypokalaemia and male prone to hyperkalemia. There is no explanation for this discrepancy but may be attributable to skeletal muscle mass difference. Other studies showed the reverse, as African patients are more likely to develop hypokalemia, due to their low aldosterone levels when compared to those of other ethnicities(12). Although patients with renal impairment taking spironolactone are expected to develop hyperkalemi with spironolactone (13). Our study showed the reverse, and that hypokalemia is more frequent. Similar findings have been reported in African Americans with HF exhibit who exhibit less hyperkalemia and more hypokalaemia with spironolactone compared with non-African Americans (14). This may be explained by the genetic variation in the RAAS. Older age groups, i.e. 50-70 years old with additional low intake of potassium and anorexia also exhibit similar finding.

8% of patients using ACEIs with renal impairment and HF had hyperkalemia, which is less than other similar studies have shown (7). ACEIs had no significant effect on serum potassium in the presence of normal renal function.

The majority of the patients had no awareness of the dietary potassium needs and consumed their regular average Sudanese diet. Analysis of the average Sudanese diet has shown that it provides sufficient daily potassium requirements(15). High potassium is commonly found in the average Sudanese dietary items. Among those with high

potassium content are tomatoes, potatoes, okra, meat, bananas, mango, dates, dry beans and peanut butter.

Conclusion:

Serum potassium changes are not common among cardiac patients taking ACEIs, ARBs, and diuretics. Hyperkalaemia due to ACEIs only occurs in the patient with an abnormal renal function, such an effect was not seen on ARBs. Regular follow-up of serum potassium is essential in a patient with abnormal renal function taking these medications.

Study limitations:

- The medications we tested were commonly used in a heterogeneous group of patients with comorbidities. A larger sample size may be required to offset the effects of these confounding factors.
- the absence of a comparator arm
- study endpoint is a surrogate marker rather than a clinical outcome measure

Acknowledgment

We thank Mr. Ahmed Musa for entering data into SPSS and Mrs. Hind Alsanosy, the hospital dietician, for providing the dietary ingredients.

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Serum Creatinine mg/dL	**Serum Potassium mEq/l**	**ACEIs**		**ARBs**		**Furosemide**		**Spironolactone**	
		Yes	No	Yes	No	Yes	No	Yes	No
Normal ≤ 1.2 mg/dL	**2.5-3.5**	12	6	6	12	14	4	13	5
	3.6-5.5	44	27	19	52	49	22	40	31
	> 5.5	0	0	0	0	0	0	0	0
Total number of patients		56	33	25	64	63	26	53	36
P. Value		0.27		0.49		0.68		0.54	
Abnormal > 1.2 mg/dL	**2.5-3.5**	4	1	1	4	5	0	5	0
	3.6-5.5	19	4	3	20	21	2	19	4
	> 5.5	2	1	0	3	1	2	0	3
Total number of patients		25	6	4	27	27	4	24	7
P. Value		**0.046**		0.16		**0.009**		**0.009**	

Table 1. Correlation between serum potassium, serum creatinine, and ACEIs, ARBs, Furosemide and Spironolactone