# Relationship between Rasi and Hyperkalemia in Maintenance Hemodialys Patients

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**Research Article**

**Keywords:** maintenance hemodialysis, hyperkalemia, RASi

**Posted Date:** March 14th, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-1418268/v1

# Abstract

Background  Although their security in terms of serum potassium is controversial, renin-angiotensin-aldosterone system inhibitors (RASi) have greater beneficial effects on protecting relative function of the heart and kidneys than other groups of antihypertensive drugs in hemodialysis ( HD ) patients. Therefore, the aim of our study was to investigate whether medications- angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) - would affect serum potassium in chronic HD patients.

Methods  We conducted a retrospective study of 166 adults HD patients to determine which factors including RASi were connected with hyperkalemia, defined as a pre-dialysis serum potassium concentration more than 5.0 mmol/L（$K^+$） 5.0mmol/L）. And it was divided into two groups, normal group and hyperkalemia one, by the serum potassium value. Finally, we compared the differences in baseline data between two groups and explore causes leading serum potassium unstable in long-term hemodialysis patients.

Results  The median serum potassium value of all participants was 4.78 (4.28, 5.41) mmol/L, and 64 (38.6%) of them had experienced hyperkalemia. 82 (49.4%) patients were prescribed with RASi. Three variables - serum phosphorus (P 0.01), albumin (P 0.05), and using RASi (P 0.01) – were more frequent in hyperkalemia group. Multivariate logistic regression analysis showed that RASi (OR: 3.63, 95% CI: 1.78-7.40, P 0.01), serum phosphorus (OR: 2.07, 95% CI: 1.29-3.34, P 0.01),UCR (OR: 1.20, 95% CI: 1.05-1.37, P 0.01), and age (OR: 0.98, 95% CI: 0.95-0.99, P 0.05) were associated with hyperkalemia.

Conclusion  In this study, hyperkalemia is observed in 38.6% of HD patients. The use of RASi is associated with hyperkalemia in patients on prevalent HD. Also, patients with higher serum potassium or UCR and young age are likely to develop hyperkalemia during interdialysis interval.


# 1. Introduction

Maintenance hemodialysis(HD)patients are more at risk of hyperkalemia, and severe hyperkalemia is a dangerous clinical problem associated with high rates of life-threatening event and mortality including cardiac dysrhythmias and accident death[1–3]. Renin-angiotensin-aldosterone inhibitors (RASi) play an important role in lowering blood pressure and maintaining cardiorenal function[4, 5]. Since such medicines bring about the event of hyperkalemia by inhibiting aldosterone secretion, nephrologists rarely prescribe angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) to non-dialysis CKD 4–5 patients [6]. Unfortunately, knowledge of RASi influences on serum potassium concentrations is not only sparse but also controversial. Thus, the purposes of this study were to research the correlation between RASi and hyperkalemia in maintenance HD through a retrospective study.

# 2. Subjects And Methods

# 2.1 Patients selection

Between January 2018 and December 2021, we performed a retrospective study involving adult patients(≥18 years old) undergoing maintenance HD treatment. 214 patients undergoing hemodialysis treatments at The Second Affiliated Hospital of Shantou University Medical College and The Sixth Affiliated Hospital of Sun Yat-sen University, 3 times per week for a minimum of 120 days and more than 200 mL/min blood flow were eligible to participate. And exclusion criteria for patients: (i) blood transfusion within two weeks;(ii) history of potassium supplementation within two weeks;(iii) history of serious concomitant illnesse s such as shock, death or acute gastrointestinal bleeding during hospitalization ; (iv) history of admission with acute gastrointestinal bleeding and venous fistula stenosing or tremor disappearing. Ultimately, we had 166 patients included in this study. (shown in Fig. 1)

## 2.2 Study design and data collection

This retrospective study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-Sen University. Some basic clinical variables were evaluated, including age, sex, body mass index (BMI; $kg/m^2$), residual urine volume (mL/d), duration of dialysis (months), cause of end-stage renal disease (ESRD), HD modality, pre-dialysis systolic blood pressure (SBP; mmHg) and diastolic blood pressure (DBP; mmHg), the use of drug ( Loop Diuretics, Beta-blockers, CCBs, RASi and Insulins). We also recruited their laboratory data [serum potassium (mmol/L), blood urea nitrogen (mg/dl), serum creatinine (mg/dl), albumin (g/L), serum phosphorus (mmol/L), hypersensitive CRP (mg/L) and intact PTH (iPTH; pg/ml)]. Blood samples were drawn from the arterial end of the vascular access before HD after the long interdialysis interval and tested by specific standard in our hospital, but the rest information was acquired from a computerized data file. A history of hyperkalemia was defined as once or more occurrences of pre-dialysis serum potassium value>5.0 mmol/l. All patients accepted only the dialysate of same potassium concentration (2.0 mmol/L).

## 2.3 Statistical analysis

Continuous data are described as the mean values ± standard deviation or medians and interquartile ranges, while categorical data are described as precentages. Continuous variable data were compared by the t test or the Mann-Whitney nonparametric test. Categorical data were compared by the $X^2$ test. Clinically important variables that showed a trend toward statical significance ($P < 0.15$) on univariate testing were included in the multivariate models. Only variables that reached statistical significance ($P < 0.05$) were thought to be associated with hyperkalemia in maintenance HD. All tests of significance were two-side. The analyses were performed with SPSS software version 26.0.

# 3. Results

There were 214 maintenance HD patients eligible for our study. A total of twenty-six patients were not enrolled because they need a transfusion (14 patients) or complement the potassium treatment (12 patients) additionally. Also, of the twenty-two patients who did not follow the study, eight patients because of death, seven patients because of acute gastrointestinal bleeding occurring in or outside the

hospital , four suffering from shock and three venous fistula stenosing or tremor disappearing. Finally, only 166 patients remained.

At baseline, the median dialysis duration of whole patients was 24.00 (10.75, 48.00) months, and the median pre-dialysis serum potassium levels was 4.78 (4.28, 5.41) mmol/L, of which 102 (61.4%) were in the normal group but 64 (38.6%) in increased potassium one. The median age was 60 (49, 70) years. Female was 36.7% and male 63.3%. Causes of end-stage renal disease mainly consists of diabetic nephropathy (39.8%) and chronic glomerulonephritis (28.9%). 112 (67.5%) HD patients use arteriovenous fistulas. 75.9% were taking CCBs, 49.4% RASi and 39.8% Beta-blockers. (shown in Table 1)

Patients in hyperkalemia group were younger than those serum potassium levels stay in stable range, and an arteriovenous fistula treatment was present in 73.4% of HD patients with hyperkalemia, although neither was statistically significant. Besides, median ratios of blood urea nitrogen/serum creatinine (UCR) were similar in both groups ($p>0.05$). The use of RASi ($P < 0.01$), albumin ($P < 0.05$) and serum phosphorus levels ($P < 0.01$) was significantly higher in hyperkalemia group (shown in Table 1). Seven variables (including age, serum phosphorus, UCR, Loop Diuretics, Beta-blockers, RASi and Insulins) on univariate logistic testing qualified for inclusion in multi-factor analyses (P 0.15). At last multivariate regression analysis showed that age (OR: 0.98, 95% CI: 0.95-0.99, P 0.05), UCR (OR: 1.20, 95% CI: 1.05-1.37, P 0.01), serum phosphorus (OR: 2.07, 95% CI: 1.29-3.34, P 0.01) and RASi (OR: 3.63, 95% CI: 1.78-7.40, P 0.01) were independently associated with an increased risk of developing hyperkalemia in maintenance hemodialysis (shown in Table 2).

**Table 1 Comparison of baseline characteristic between groups**

| | Serum K | | |
|---|---|---|---|
| Variable | ≤5.0mmol/l（N=102） | （5.0mmol/l）N=64） | P-Value |
| Sex (%) | | | 0.864 |
| Male | 62.7% | 64.1% | |
| Female | 37.3% | 35.9% | |
| Age (years) | 64 (50, 71) | 57±16 | 0.090 |
| BMI (kg/m $^2$ )* | 21.4±3.4 | 21.6 (19.5, 24.2) | 0.52 |
| SBP (mmHg) | 148±21 | 152±21 | 0.155 |
| DBP (mmHg) | 82(70,91) | 85(73,94) | 0.167 |
| History of Dialysis (years) | 2.00 (0.75, 4.00) | 2.00 (1.00, 4.75) | 0.639 |
| Residual Urine Volume (ml/d) | 5 (0, 235) | 0 (0, 282) | 0.763 |
| Serum Phosphorus (mmol/l) | 1.85 (1.31, 2.29) | 2.27±0.77 | <0.01 |
| BUN/Creatinine ratio | 5.93 (4.72, 7.38) | 6.23 (5.33, 8.10) | 0.174 |
| Albumin(g/L) | 36.82 (32.89, 39.35) | 37.74±4.93 | 0.048 |
| hs-CRP(mg/L) | 9.36 (2.70, 19.40) | 6.18 (1.53, 19.40) | 0.231 |
| Intact PTH (pmol/L) | 266.25 (79.78, 620.21) | 371.1 (120.9, 620.21) | 0.212 |
| Drugs | | | |
| Use of Loop Diuretics | 4.9% | 12.5% | 0.076 |
| Use of Beta-blockers | 35.3% | 46.9% | 0.138 |
| Use of CCBs | 73.5% | 79.7% | 0.367 |
| Use of ACEIs/ARBs * | 39.2% | 65.6% | <0.01 |
| Use of Insulins | 26.5% | 37.5% | 0.134 |
| Use of AVF | 63.7% | 73.4% | |
| History of Kidney Disease | | | |
| Hypertensive Renal Disease | 15.7% | 10.9% | |
| Diabetic Nephropathy | 35.3% | 46.9% | |
| Chronic Glomerulonephritis | 27.5% | 31.3% | |
| Other Kidney Disease | 21.6% | 10.9% | |

* BMI: body-mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; hs-CRP: hypersensitive C-reactive protein; CCB: calcium channel blockers; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; AVF: internal arteriovenous fistula

**Table 2 Indepent risk factors for hyperkalemia in maintenance hemodialysis patient and OR(95%CI) values for each factor**

| Variables | OB | Lower | Upper | OB (95% CI) | P Value |
|---|---|---|---|---|---|
| Age（years） | 0.975 | 0.951 | 0.999 | 0.975 (0.951-0.999) | 0.046 |
| BUN/Creatinine ratio | 1.202 | 1.054 | 1.372 | 1.202 (1.054-1.372) | 0.006 |
| Serum Phosphorus（mmol/l） | 2.072 | 1.285 | 3.34 | 2.072 (1.285-3.340) | 0.003 |
| *Use of ACEIs/ARBs | 3.63 | 1.78 | 7.402 | 3.630 (1.780-7.402) | 0.0004 |

* ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker

# 4. Discussion

An increasing number of studies have proved ACEIs/ARBs outweigh other types of antihypertensive drug in reducing the risk of adverse cardiovascular events as well as death by maintaining cardiorenal function in CKD patients. Nephrologists usually start choosing RASi for patients whose kidney function enter the early stage of CKD, even continue to use them in those with ESRD. Therefore, such medicines are widely used in the hemodialysis population[5, 7, 8]. Regretfully, through interfering with angiotensin-converting enzyme or angiotensin II receptor, RASi may inhibit renal potassium excretion so that accumulate potassium mostly in the human body [6, 9]. Moreover, residual urine output is also correlated to electrolyte homeostasis. The potassium of anuric patients has prone to be disordered than that of nonanuric patients. As the serum potassium is rising, major adverse cardiovascular events(such as sinus bradycardia, atrioventricular block, ventricular fibrillation, and asystole)are mainly causes threating life of HD patients[1, 3, 10]. To prevent fateful clinical incident, 12% physicians intentionally discontinue these prescriptions in HD patients with hyperkalemia[11]. In view of lacking enough literatures evaluating the safety and efficacy of ACEIs/ARBs therapy in long-term HD patients, we conducted a retrospective study on patients who received dialysis 3 times a week and had more than 120 days of dialysis duration. Then we would observe what effect of RASi had on serum potassium. Patients in hyperkalemia group were more likely to be treated with RASi and some of them even happened severe hyperkalemia. The result is consistent with previous studies of the effects of RASi on the potassium excretion in HD patients[10, 12]. The results of both studies confirm that this variable is an independent factor influencing hyperkalemia in patients with long-term hemodialysis. And anuric patients are more likely to develop hyperkalemia, but that the residual urine output may not plays an interaction with drugs. Before or after the introduction of

any type of RASi, the systolic and diastolic blood pressure levels seem not significantly change in anuric patients, also the finding in the magnitude of the serum potassium concentrations increment is similar[12].

However, one study published in 2007 found that the use of ACEIs/ARBs was not independently associated with an increased risk of developing hyperkalemia in maintenance HD patients[13]. Han[13] used a prospective crossover study in which all participants underwent nutritional education (guaranteed daily intake of potassium 60 mmol/L and sodium less than 100 mmol/L) and verification their adherence of dietary and medication. In addition, he compared patients' basic and average serum potassium changes monthly until the end of study. It is strict management of diet and observation of dynamic serum potassium changes after using RASi that led to contradictory findings. But this is also similar to our conclusions that nutritional status or daily diet have an impact on serum potassium levels in chronic HD patients.

Although there is little association between serum potassium and age, patients with hyperkalemia were younger and reached higher serum phosphorus levels than the normal group. Phosphorus mainly comes from food, especially protein. Poor diets meeting the appetites of young patients are fried or processed foods, carbonated drinks, and seafood. It is a pity that these foods with high phosphorus content threaten the homeostasis of serum potassium during interdialysis[14]. Zhao and Zuo [15]believed that high serum phosphorus may approximately equal to inadequate hemodialysis. What the adequate dialysis largely depends on is the frequency of renal replacement therapy. Generally, greater-than-equal 3 times/week is more conducive to the physiological fluctuation of serum potassium. In addition, UCR was other obvious factor to induce hyperkalemia on stable patients on maintenance hemodialysis. Not only can this ratio reflect the nutritional status of patients, it also be used to estimate the amount of ingested protein daily[16]. We speculate that patients with higher UCR may have a good appetite. As the risk of hyperkalemia among HD patients was greater in those intaking more phosphorus-containing foods and getting higher UCR, we should optimize the management of dietary patterns in HD patients with better nutritional status.

Based on the above discussions, serum potassium still exceeds easily out of the ideal range in regular maintenance hemodialysis patients using RASi; unreasonable dietary intake would cause hemodialysis population complicated with hyperkalemia likewise. Hence, hyperkalemia can be improved by regulating daily potassium consumption and prescribing drug rational to prevent HD patients’ life from facing threatening.

Our study had some limitations: Firstly, it is hard for us to control confounding factors like KT/V ≥ 1.2 and per dialysis session over four hours among entire maintenance hemodialysis patients. Secondly, we cannot measure and assess the accurate potassium contenting in patients' meals.

# 5. Conclusion

In a nutshell, the retrospective study found that a complication of hyperkalemia was present in 38.6% of maintenance hemodialysis patients. RASi, serum phosphorus, UCR and age are significantly related to hyperkalemia in hemodialysis population. Aiming to avoid hyperkalemia occurring, we suggest that patients with interdialysis hyperpotassium, especially those with recurrent tendency, need to stabilize ion potassium levels by adjusting diet structure and using RASi treatment rationally.

# Abbreviations

1. RASi: renin-angiotensin-aldosterone system inhibitors
2. HD : hemodialysis
3. ACEI: angiotensin-converting enzyme inhibitoror
4. ARB: angiotensin II receptor blocker
5. ESRD : end-stage renal disease
6. SBP :systolic blood pressure
7. DBP: diastolic blood pressure
8. UCR: ratios of blood urea nitrogen/serum creatinine
9. BMI: body-mass index
10. hs-CRP: hypersensitive C-reactive protein
11. CCB: calcium channel blocker
12. AVF: internal arteriovenous fistula

# Declarations


### Acknowledgement

The authors thank Yimin Zhang for comments and critical reading of the manuscript.


### Author contributions

Yimin Zhang and Xiaochang Xu contributed to the study conception and design.  Guitian Hong, Zeen Xiao, and Yejing Dong contributed to the acquisition of materials and data. Shiting He and Weiji Xie contributed to analysis and interpretation of the data. The first draft of the manuscript was written by Shiting He, and all authors commented and revised on previous versions of the manuscript. All authors read and approved the final manuscript.


### Funding

None.


### Availability of data and materials

All data generated or analyzed during the current study available from the corresponding author on reasonable request.

### Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Research Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (protocol reference number E2022016).Due to the retrospective nature of the study, written informed consent for participation in the study was waived by the Research Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University.

### Consent for publication

Not applicable.

### Conflict of interest statement

The authors declare that they have no competing interests.

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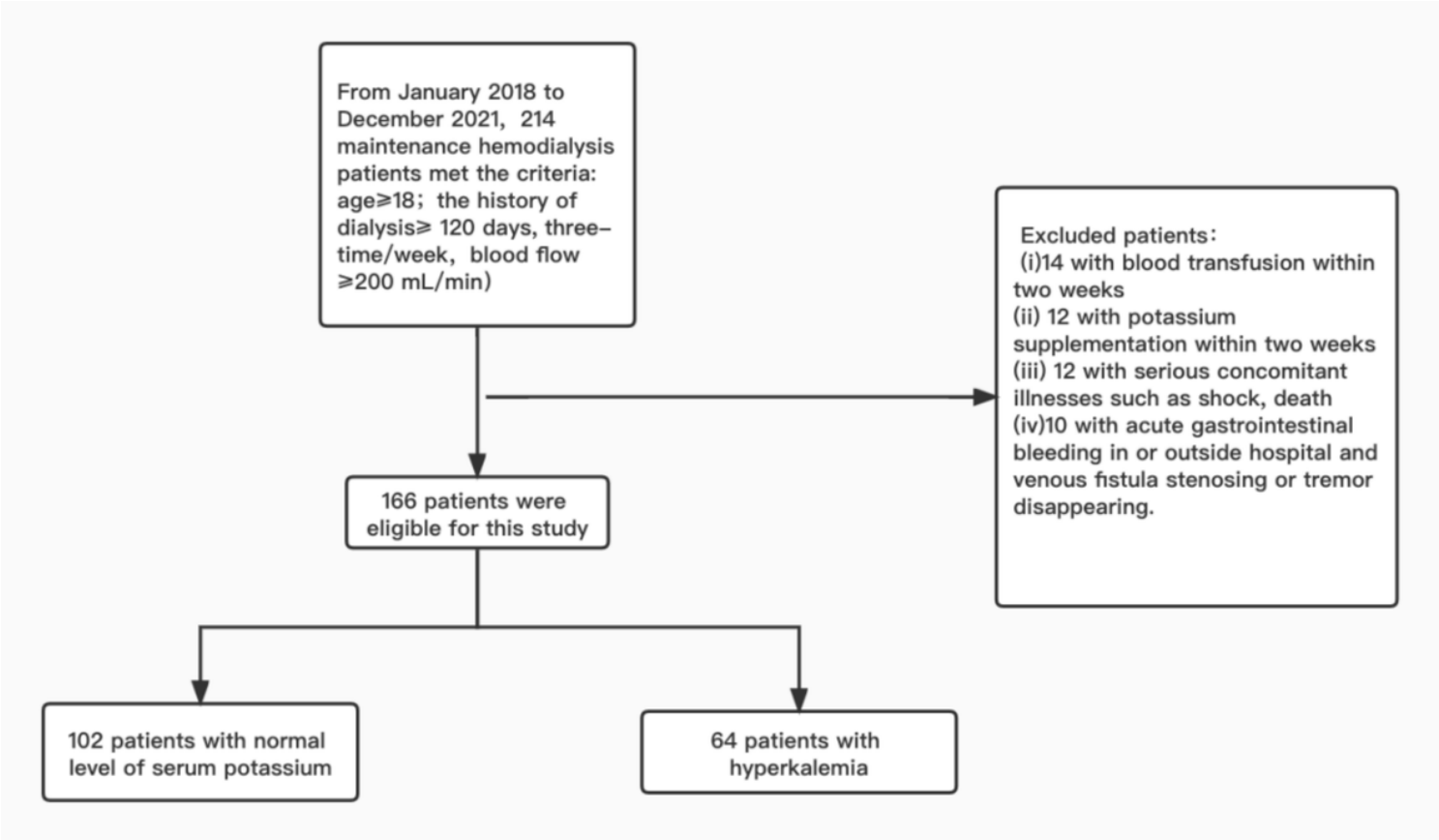
# Figures



## Figure 1

## Flowchart for inclusion criteria, exclusion criteria and patient grouping