Revista Colombiana de Nefrología
Vol. 13, Núm. 1 (2026) - Publicación continua
http://doi.org/10.22265/acnef.13.1.818

Original article

Serum and urine electrolyte and nitrogenous waste product changes during the renal functional reserve test

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How to cite: Musso CG, Juarez R, Gonzalez-Torres H, Capotondo M, Terrasa S, Aroca-Martinez G. Serum and urine electrolyte and nitrogenous waste product changes during the renal functional reserve test. Rev. Colomb. Nefrol. 2026; **13**(1), **e818**. https://doi.org/10.22265/acnef.13.1.818

Submitted: 08/Apr/2024
Accepted: 10/Jan/2025
Published: 04/Feb/2026

Abstract

Context: Renal functional reserve (RFR) refers to the kidney's capability to increase its basal glomerular filtration rate (GFR) by at least 20 % after an adequate stimulus, such as a protein overload. As far as we know, no studies have yet reported the behavior of electrolyte excretion during the renal functional reserve test.

Material and methods: A prospective study to evaluate serum and urinary changes in electrolytes, nitrogenous waste products, glucose, protein, and albumin during the renal functional reserve test in healthy young adults, evaluating their cimetidine-aided creatinine clearance and renal functional reserve test (Hellerstein).

Keywords: Renal reserve, Electrolytes, Renal physiology, Kidney, Glomerular filtration rate, Prospective studies.

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E-ISSN: 2500-5006/L-ISSN: 2389-7708

Results: There was a statistically significant increase in glomerular filtration rate (positive renal functional reserve) and serum glucose, as well as a significant reduction in serum values of nitrogen derivatives and electrolytes in 46 healthy young adult volunteers during the renal functional reserve test. Regarding the urinary fractional excretion of these substances, significant increases were observed for nitrogenous waste products and electrolytes, except for phosphorus, glucose, protein, and albumin urinary excretion, which suffered no change.
Conclusion: The renal functional reserve significantly modified not only glomerular filtration rate but also nitrogenous waste products and electrolyte serum levels, as well as their urinary fractional excretion values in healthy young adults (mean age: 35 years).

Cambios en los electrolitos séricos y urinarios y en los productos de desecho nitrogenados durante la prueba de reserva funcional renal

Resumen

Contexto: la reserva funcional renal (RFR) es la capacidad del riñón para aumentar su tasa de filtración glomerular basal (TFG) hasta al menos un 20 % tras un estímulo adecuado, como una sobrecarga proteica. Hasta donde sabemos, aún no se ha descrito qué ocurre con la excreción de electrolitos durante la prueba de reserva funcional renal.
Material y métodos: estudio prospectivo para evaluar los cambios en los electrolitos séricos y urinarios, productos de desecho nitrogenados, glucosa, proteínas y albúmina durante la prueba de reserva funcional renal en adultos jóvenes sanos, evaluando su aclaramiento de creatinina con cimetidina y la prueba de reserva funcional renal (Hellerstein).
Resultados: se observó un aumento estadísticamente significativo de la tasa de filtración glomerular (reserva funcional renal positiva) y de la glucosa sérica, así como una reducción significativa de los valores séricos de derivados nitrogenados y electrolitos en 46 voluntarios adultos jóvenes sanos durante la prueba de reserva funcional renal. En cuanto a la excreción fraccional urinaria de estas sustancias, se observó un aumento significativo de los productos de desecho nitrogenados y de los electrolitos, con excepción de la excreción urinaria del fósforo, la glucosa, las proteínas y la albúmina, la cual no presentó cambios.
Conclusión: la reserva renal modificó significativamente no solo la tasa de filtración glomerular, sino también los niveles séricos de los productos de desecho nitrogenados y de los electrolitos, así como sus valores de excreción fraccional urinaria, en adultos jóvenes sanos (edad media: 35 años).

Palabras clave: reserva renal, electrolitos, fisiología renal, riñón, tasa de filtración glomerular, estudios prospectivos.

Introduction

Renal functional reserve (RFR) is classically defined as the kidney's capability to increase its basal glomerular filtration rate (GFR) by at least 20 % after an adequate stimulus, such as an oral protein or intravenous amino acid overload [1–6]. It is generally accepted that the amino

acid components of ingested protein, or infused amino acids per se, induce the renal response through intrarenal vasodilatation, with the consequent development of hyperfiltration. The renal response to protein or amino acid load is attributed to the tubular-glomerular feedback (TGF) mechanism activation. In this sense, it has been postulated that specialized cells in the walls of the distal tubule, known as *macula densa*, sense a tubular flow-related signal (such as urine sodium, chloride concentration, or transport rate) and sends an order to the afferent arteriole to induce vasoconstriction or vasodilation in response to changes in this signal. An increase in plasma amino acid levels would result in an increase in the filtered load of amino acids which would provoke an increase in tubular amino acid reabsorption [7–9]. Since amino acids and sodium are cotransported in the proximal tubule, proximal sodium (chloride) reabsorption would also increase, resulting in a decrease in sodium (chloride) delivery to the distal tubule and *macula densa.* The TGF mechanism results in afferent arteriolar vasodilatation and, consequently, to increases in renal blood flow and GFR. This vasodilatory phenomenon could be induced by local prostaglandins, nitric oxide, and/or kinin release [10–12].

The most effective, simple, and reliable method for evaluating GFR seems to be the cimetidine-aided creatinine clearance (CACC), particularly when oral cimetidine is used. Since cimetidine inhibits creatinine secretion in the proximal tubules, the ratio between CACC and GFR is about 1.1. For creatinine tubular secretion blockade to be effective, an adequate dose of cimetidine (1600 mg/day) should be administered for at least two days before creatinine clearance measurement [2–4].

It is known that hyperfiltration can increase the excretion of substances capable of being freely filtered (totally or mostly), such as electrolytes and nitrogenous waste products [5]. However, as far as we know, the serum and urinary changes in electrolytes (sodium, chloride, potassium, calcium, phosphate, and magnesium) and nitrogenous waste products (urea and uric acid) during the RFR test in healthy individuals have not yet been reported. Therefore, it was decided to undertake an original evaluation of these parameters.

Material and methods

A prospective study was carried out in order to evaluate the serum and urinary changes in electrolytes and nitrogenous waste products, as well as glucose, protein, and albumin levels during the RFR test in healthy ambulatory young adults (18-50 years of age). Participants were sequentially recruited while being evaluated as potential kidney donors at Clínica de la Costa, Barranquilla, Colombia, in 2023. The study inclusion and exclusion criteria were as follows:

Inclusion criteria

- Resting GFR $\geq$ 80 mL/min/1.73m^2, determined by measured creatinine clearance.

Exclusion criteria

- Age <18 or >50 years.
- Presence of cardiovascular disease, diabetes mellitus, hypothyroidism, nephropathy, cirrhosis, or respiratory disease, and/or current use of medication.

These conditions were excluded based on normal physical examination, subjective global assessment, electrocardiogram, serum creatinine, urea, cholesterol, albumin, hepatic enzymes, thyroid hormones, and urinalysis, as well as normal cardiac, hepatic, and renal ultrasound in all the volunteers.

Negative to participate

In each volunteer, resting GFR was first measured by using cimetidine-aided creatinine clearance (CACC), followed by an RFR test as described by Hellerstein *et al.* [6]. To measure RFR, the following protocol was applied [2]: each volunteer followed a low-protein diet (0.8 g/kg/day) for two weeks (as prescribed by a nutritionist) and received oral cimetidine at a dose of 800 mg (four tablets) every 12 hours during the 48 hours prior to the RFR test.

Initially, a basal blood sample was obtained, after which oral hydration was initiated using tap water (20 mL/kg) during 30 minutes. After bladder voiding, the time and volume data from each micturition were documented for two periods. Based on these data, CACC was calculated by applying the following formula:

CACC = [urinary creatinine $\times$ urine volume (mL) / serum creatinine $\times$ time (min)]

Finally, the two CACC values were averaged to calculate the basal GFR for each volunteer. In addition, average fractional excretion (FE) values for electrolytes and nitrogenous waste products (basal FE) were also obtained for each volunteer.

Subsequently, each participant received an oral protein load of 1.5 g/kg body weight, based on a milk and cheese meal (30 minutes for ingestion and 40 minutes for digestion). After bladder voiding, four consecutive blood samples were collected (30, 60, 90, and 120 minutes), along with urine samples (including their time and volume) from each micturition, over a two-hour period (with voiding occurring every 30-40 minutes).

From the obtained blood and urine samples, sodium, chloride, potassium, calcium, phosphorus, magnesium, glucose, protein, albumin, urea, and uric acid levels were measured.

Based on the data, the maximum CACC value after the protein load (peak GFR), as well as the maximum electrolytes and nitrogenous waste products FE values (peak FE), were obtained. In addition, the delta CACC value (peak CACC – basal CACC), delta FE for electrolytes and nitrogenous waste products (peak FE – basal FE), and delta urinary glucose, protein, and albumin values were calculated. Statistical analysis was performed using the ANOVA test.

Results

In the present study, RFR was evaluated in 46 Caucasian adults with a mean age of 35 years (range: 20-50 years) and a male-to-female ratio of 1.3. A statistically significant increase in serum glucose levels and glomerular filtration rate was documented during the RFR test, indicating a positive RFR. No adverse events were observed. Additionally, there was a significant reduction in serum values of nitrogenous waste products (urea and uric acid), as well as in electrolytes (sodium, potassium, chlorine, calcium, magnesium, and phosphorus) in healthy volunteers. It is worth mentioning that all these peak values were within the normal range (Table 1).

Table 1. Basal serum values, peak values, delta values, time to peak, and statistical differences between peak and basal measurements during the renal functional reserve test

Serum values	Basal value X±SD	Peak value X±SD	Delta value X±SD	Time (min)	P value
Creatinine (mg/dL)	0.9±0.1	0.8±0.1	-0.1±0.05	77±37	0.0001
Urea (mg/dL)	27±8.4	26±8	-1.4±2	46±31	0.0001
Uric Acid (mg/dL)	4.9±1	4.5±1	-0.4±0.4	81±39	0.0001
Sodium (mmol/L)	139±2	136±2	-2.6±2	68±36	0.0001
Potassium (mmol/L)	4.1±0.4	3.7±0.4	-0.3±0.3	52±33	0.0001
Chloride (mmol/L)	103±3	102±3	-0.9±2	70±32	0.001

Calcium (mg/dL)	9.1±0.4	8.8±0.5	-0.4±0.4	43±25	0.0001
Phosphorus (mg/dL)	3.8±0.6	3.2±0.5	-0.6±0.4	43±24	0.0001
	2.1±0.2	1.9±0.2	-0.2±0.2	57±35	0.0001
Glucose (mg/dL)	73±13	83±18	10±13	84±37	0.0001

Source: Own elaboration.

Regarding the urine FE of the above-mentioned substances, there was a statistically significant increase in urine FE for nitrogenous waste products (urea, uric acid) and most of the electrolytes (sodium, potassium, chlorine, magnesium), while there was no significant increase in phosphorus, glucose, protein, and albumin urinary excretion during the RFR test (Table 2).

Table 2. Fractional excretion (FE) and cimetidine-aided creatinine clearance (CACC): Basal and valley values in renal reserve test

	Basal value X±SD	**Peak value X±SD**	**Delta value X±SD**	**Time (min)**	**P Value**
CACC (mL/min)	113.8 ± 37.9	173,1±76.8	60.3 ± 38.9	77±37	0.0001
RFR (%)	–	–	57±45.4	77±37	–
FE Urea (%)	45±15	109±1.5	0.6±1.4	82±37	0.004
FE Uric Acid (%)	6±2.5	11.5±3.3	5.2±3.4	90±36	0.0001
FE Sodium (%)	0.7±0.5	1.2±1.2	0.5±1.1	92±34	0.004
FE Potassium (%)	6.6±3.2	13±8.7	6.4±8.9	84±39	0.0001
FE Chloride (%)	0.8±0.7	2.2±2.9	1.4±2.7	86±35	0.001
FE Calcium (%)	1.1±0.8	2.8±1.2	1.6±1.5	84±32	0.0001
FE Phosphorus (%)	14±5.8	13±10	-0.4±10	62±35	0.76

FE Magnesium (%)	3.1±1.7	5.6±2.3	1.8±2.3	81±29	0.0001
Urinary Glucose (mg/dL)	0.1±0.6	0.2±1	0.05±0.4	49±33	0.9
Urinary Protein (mg/dL)	0.1±0.2	0.05±0.1	-0.06±0.1	44±29	0.8
Urinary Albumin (mg/dL)	20±46	17±55	-0.3±49	43±27	0.9

Source: Own elaboration.

Finally, peak urinary FE of nitrogenous waste products and electrolytes was reached between 77 and 92 minutes during the RFR test (total evaluation period: 120 minutes). The timing of these peak FE values was similar to that of the peak RFR value (77 minutes).

Discussion

RFR is classically defined as the kidney's capability to increase its basal GFR by at least 20 % after an adequate stimulus, such as oral meat or intravenous amino acid supply [1, 7]. These RFR-inducing mechanisms explain the positive RFR value (57±45.4 %) documented in our study.

The significant reduction in serum concentration of urea, uric acid, sodium, chloride, potassium, magnesium, and calcium documented during RFR in our study could be explained by the significant increase in urinary excretion of these substances during the RFR test. In turn, this increased urine excretion can be attributed to at least two mechanisms. On one hand, hyperfiltration induced by oral protein overload leads to increased glomerular filtration and, therefore, higher urinary excretion of these substances, since they are totally (urea, sodium, chlorine, potassium) or almost totally filterable (uric acid, calcium, magnesium) due to their small molecular size and minimal or absent serum protein binding [5]. On the other hand, the overhydration provoked during the RFR test increases tubular urine flow, thereby reducing tubular reabsorptive capability and further increasing urinary excretion of the aforementioned substances [13]. Moreover, this induced overhydration could also explain the significant reduction in serum sodium levels observed during the test [5].

It should be noted that the only serum variable that increased during the test was blood glucose. This phenomenon can be readily explained by the comparison between postprandial and fasting serum glucose levels. Conversely, variables such as glycosuria, proteinuria, and albuminuria did not change throughout the test, as they remained at zero values, consistent with the healthy status of the individuals. Regarding phosphorus values, a significant reduction in serum levels was observed without a corresponding significant increase in urinary excretion. Given that insulin can induce phosphorus entry into the intracellular compartment, perhaps the observed serum phosphorus reduction during the postprandial period of the test could be attributed to an internal balance mechanism (phosphorus shift) [5].

Conclusion

RFR significantly modified not only GFR but also the serum levels of nitrogenous waste products and electrolytes, as well as their urinary fractional excretion values, in 46 healthy young adult individuals.

Authors contribution

Carlos G. Musso: Conceptualization, drafting, revision, and editing; Gustavo Aroca-Martínez: Data curation, project management, resources, and software; Sergio Terrasa: Formal analysis, methodology, and validation; Henry González-Torres: Formal analysis, methodology, and visualization; Rossina Juárez: Research and supervision; and María M. Capotondo: Drafting.

Ethical statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (acta 2023-0004-03.02.2023) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from each volunteer.

Conflicts of interest

All the authors declare that they have no conflicts of interest.

Use of artificial intelligence (AI)

The authors declare that they did not use artificial intelligence in the preparation or writing of this article.

Data statement

The authors declare that there are no open access data for this article. Any questions regarding this matter should be directed to the corresponding author.

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