Comparison of Different Methods of Glomerular Filtration Rate in Young Males with Arterial Hypertension

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Abstract —Glomerular filtration rate (GFR) was investigated with different methods in hypertensive young men (18-27 years) who never had primary disease of the kidney. GFR was evaluated by Rehberg method, Cockcroft-Gault formula, MDRD (Modification of diet in renal disease) formula, MDPvD (methylenedioxypyrovalerone) formula, CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. The normalization of GFR to a standardized body surface area of 1.73 m2. The study showed no significant difference in the mean values of GFR calculated by Rehberg and Cockcroft-Gault formula. The GFR obtained by MDRD, MDPvD, CKD-EPI were respectively lower by 15.5%, 15.6% and 10.0%, compared with the result of the Rehberg method. Similar result was obtained when compared with the values calculated by the Cokcroft-Gault formula: GFR calculated by MDRD, MDPvD, CKD-EPI were respectively lower by 16.0%, 16.1% and 10.4%, respectively. In conclusion, GFR can better be determined in first degree hypertensive patients using Rehberg method or the Cokcroft Gault formula.

Keywords—Glomerular filtration rate; Cockcroft-Gault; MDRD; MDPvD; CKD-EPI

1 Introduction

It is important to determine serum creatinine level and calculate the glomerular filtration rate (GFR) in all patients with arterial hypertension, since renal damage in hypertension is a strong and frequently occurring predictor of cardiovascular disease and mortality [1]. GFR can be calculated from the results of the Rehberg test [2] after determination of urine and plasma serum creatinine levels or according to formulae based on only one setting of plasma creatinine [1, 3, 4]. The formula Cokcroft-Gault, widely known for calculating GFR, takes into account, along with the level of creatinine in the blood, the age, body weight and sex of the patient [5, 6]. In recent years, shortened formulae (also known as express formulae) for calculating GFR are widely recommended for use: MDRD (Modification of diet in renal disease), MDPvD (methylenedioxypyrovalerone), CKD-EPI (Chronic Kidney Disease EpidemiologyCollaboration) [1, 3, 7]. However, there is convincing evidence that the calculation of GFR using express formulae (MDRD, MDPvD, CKD-EPI) is unacceptable in the following situations [4, 8]: 1) body size and muscle mass of the patient abruptly deviate from the mean values (body-builders, patients with amputation of the limbs); 2) severe exhaustion and obesity (BMI < 15 and > 40 kg / m^2); 3) pregnancy; 4) diseases of skeletal musculature (myodystrophy); 5) paralysis/paresis of limbs; 6) individuals on a vegetarian diet; 7) rapid decrease in renal function (acute or rapidly progressive nephritic syndrome); 8) renal replacement therapy; 9) post-kidney transplantation.

The aim of this study was to compare the GFR determined by different methods in males with a history of hypertension, but without primary kidney diseases or signs of renal insufficiency. Furthermore, we compare GFR calculated by Cokcroft-Gault, MDRD, MDPvD, CKD-EPI and their normalized results to 1.73 m^2 with GFR, calculated by the traditional Rehberg method in the same group of hypertensive patients.

2 Methods

The study protocol was approved by the ethics and research committee of the Belarusian State Medical University, Minsk, Belarus. The participants for this study were who have been previously diagnosed with first degree hypertension and who have routine visits to the outpatient clinic of the cardiology department of the 6th-Hospital of the Belarusian State Medical University. The intended patients were randomly selected and explained the study aims and objectives. Only those who agreed gave consent for participation in the study.

The study included 32 men who were diagnosed with arterial hypertension. The average age of the patients was 22.7 years (18–27 years). 30 participants had first-degree hypertension, whereas 2 participants had II degree hypertension.

A. Exclusion Criteria

The exclusion criteria for this study were as follows:

1. Unwillingness to participate in the study.
2. A sharp deviation from the normal body mass index (BMI).
3. Severe exhaustion and obesity (BMI <15 and> 40 kg / m^2).
4. Consumption of the vegetarian diet by the participants.

B. Characteristics of the Patients

Information on case histories of each patient was retrieved. All patients were examined. The data gathered were grouped according to the following: sex, age, height, body weight, blood creatinine level, Rehberg test result, and their clinical diagnosis. To confirm the validity of the diagnosis, results of microalbuminuria, 24-hour blood pressure monitoring, lipidogram, BMI calculation, and anamnesis data were obtained. There was no microalbuminuria in the examined participants. Excess BMI was recorded in 10 participants. Disorder of lipid metabolism was detected in 6 participants. There were no other concomitant diseases in the examined persons.

C. Determination of GFR

To ensure the correctness of the comparison, the GFR calculated using the Cokcroft-Gault formula was standardized to 1.73 m^2 of body surface area, since the MDRD, MDPvD, and CKD-EPI formulae imply such standardization. In order to unify the units of measurement, a translation of the plasma creatinine values from μmol / liter to mg / deciliter was performed. The formulae used to calculate GFR are shown below.

1. The GFR formula according to Rehberg is given as:

$$GFR = \frac{U \times V}{P}$$

Where U – urine creatinine; P – blood plasma creatinine; V – minute diuresis

The Rehberg method was used as a reference.

2. Cokcroft-Gault formula (ml/min) [6, 9]:
GFR = [(140 – age) ● (BW, kg) ● 0.85 (for women)]: [(P creatinine, μmol / L) ● 0.8g where: BW – body weight; P – plasma.
Formula for standardizing GFR by Cokcroft-Gault to 1.73 m^2 of body surface area [6, 9]:
$GFR_{standardized}$ (ml / min / 1.73 m^2) = $GFR_{initial}$ (ml / min) ● 1.73: S
Where S is the body surface area (m^2); S = 0.007184 ● height (cm)$^{0.725}$ ● body weight (kg)$^{0.425}$. The Cokcroft-Gault formula is the main formula for the calculation of GFR [1, 3]. The formula was proposed in 1976; It is simple and widely used [5, 6, 8].
3. MDRD formula (ml / min / 1.73 m^2) [6, 9]:
GFR = 186.3 ● (plasma creatinine, mg / dL)$^{-1.154}$ ● (age, years)$^{-0.203}$ ● 1.212 (for blacks) ● 0.742 (for women). The MDRD formula was obtained in the clinical study "Modification of Diet in Renal Disease". It gives insufficient accuracy of calculations in the range of values of 60-90 ml / min / 1.73 m^2), which is why its modification is often used – the formula MDPvD [4, 8].
4. Formula for converting plasma creatinine values from "μmol / L" to "mg / deciliter":
μmol / l: 88.4 = mg / deciliter.
5. MDPvD formula (ml / min / 1.73 m^2) [6, 9]:
GFR = 32788 ● (plasma creatinine, μmol / L)$^{-1.154}$ ● (age, years)$^{-0.203}$ ● 0.742 (for women).
6. CKD-EPI formula (ml/min/1.73 m^2) [6]:
GFR = a ● [plasma creatinine (μmol/L) **:** b]^{C} ● 0.993^{age}
The coefficients of the CKD-EPI formula depend on the sex and level of plasma creatinine (Table 1). The CKD-EPI formula is widely used as express formula for calculating GFR. It is recommended for use as the most suitable screening method for assessing GFR in outpatient and clinical practice, including patients with arterial hypertension [6, 9].

The choice of the above-mentioned formulae, for which a single laboratory indicator was required – the level of the blood creatinine – allowed for comparison on the selected group of patients.

The MDRD, MDPvD, CKD-EPI formulae are used to classify chronic kidney injury (CKI) [4, 8]. These formulae are recommended for express calculation of GFR in cardiological practice [3, 6]. CKI reflects the presence of kidney damage. The criteria for CKI are: the presence of markers of kidney damage for more than 3 months (or any markers of irreversible structural damage,

detected once) with or without a decrease in GFR; Or a decrease in GFR of less than 60 ml / min lasting more than 3 months with or without kidney damage [4, 8]. In the following classification of CKI K/DOQI 2006 (Table 1), the first stage of CKI may not detect a decrease in GFR.

D. Statistics

Excel 2010 was used for GFR calculation as well as statistical analysis of the results. The Student's t-test was applied and the level of significance was set at $p < 0.05$

3. Results and Discussion

The results of the study in young male patients with a short history of arterial hypertension without kidney damage (no microalbuminuria) show no difference on the GFR. Figure 1 shows the result of Rehberg and Cokcroft-Gault formula.

TABLE I. VALUES OF THE COEFFICIENTS OF THE CKD-EPI FORMULA

Sex	**a**	**b**	**c, depend on plasma creatinine**	
			≤ 62 µmole/L	***> 62 µmole/L***
Female	144	61.9	-0.329	-1.209
Male	141	79.6	-0.411	-1.209

TABLE II. CLASSIFICATION OF CHRONIC KIDNEY DISEASE K / DOQI 2006 [1, 4]

Stage	**Characteristics**	**GFR ml/min /1.73 m^2**
1	Kidney damage with normal or elevated GFR	> 90
2	Kidney damage with mild decline in GFR	60-89
3	Moderate decline in GFR	30-59
4	Severe decline in GFR	15-29
5	Renal insufficiency	<15

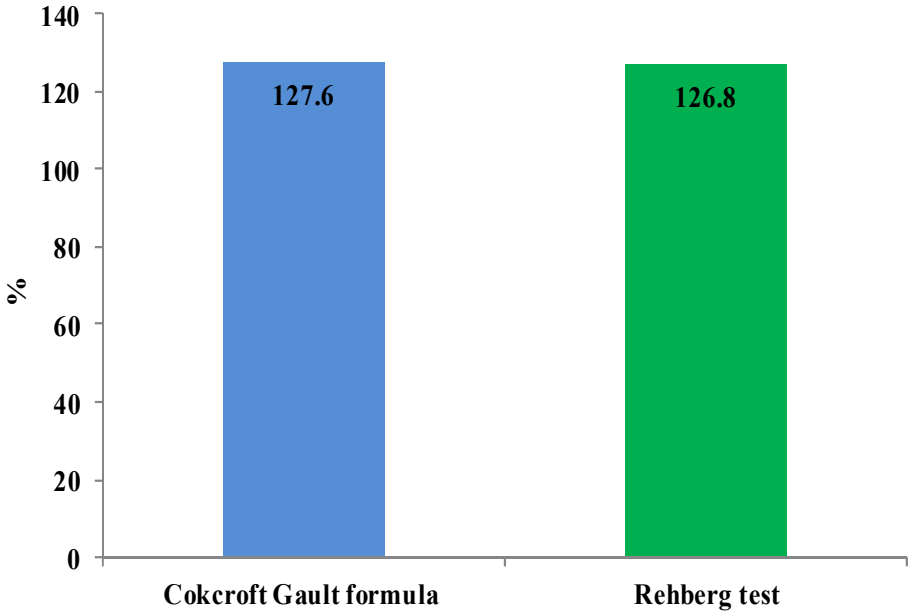

Fig. 1. GFR (ml / min), determined with the help of the Rehberg test and calculated according to the Cokcroft-Gault.

TABLE III. PARAMETERS OF GFR IN PATIENTS WITH ARTERIAL HYPERTENSION, OBTAINED BY PERFORMING REHBERG TEST, AND CALCULATED IN THE SAME PATIENTS USING EXPRESS FORMULAE.

№	Methods of calculating GFR	GFR, M±m	Significance in relation to GFR_1		% of GFR_1	% of GFR_2
1	Rehberg (ml/min/1.73m^2) - GFR_1	105.7±3.6			100	
2	Формула Cokcroft Gault (ml/min/1.73m^2) – GFR_2	106.3±2.8	t_{2-1}=0.110	p>0.05	100.6	100
3	MDRD – GFR_3 (ml/min/1.73m^2)	89.3±2.1*▲	t_{3-1}=3.905 t_{3-2}=4.816	p<0.001 p<0.001	84.5*	84.0▲
4	MDPvD – GFR_4 (ml/min/1.73m^2)	89.2±2.1*▲	t_{4-1}=3.928 t_{4-2}=4.841	p<0.001 p<0.001	84.4*	83.9▲
3	CKD-EPI – GFR_3 (ml/min/1.73m^2)	95.2±2.4*▲	t_{3-1}=2.431 t_{3-2}=2.846	p<0.05 p<0.025	90.0*	89.6▲

Our study (Table 3) showed that in young patients with a short history of 1 and 2 degrees arterial hypertension without microalbuminuria (i.e. without kidney damage), GFR calculated according to the MDRD formula is less than 90 ml / min / 1.73 m^2 and corresponds to 2-nd stage of CKI. The calculation of GFR using the MDRD formula in these young patients understated GFR value by 15.5% ($p < 0.001$) when compared to the results of the Rehberg test and by 16.0% ($p < 0.001$) compared to the result of the Cokcroft-Gault formula. Calculation of GFR by the modified (MDRD) formula MDPvD (Table 2) showed a similar picture – a 15.6% underestimation of the GFR result ($p < 0.001$) and 16.1% ($p < 0.001$) of GFR calculated by the Rehberg method and the Cockcroft-Gault formula, respectively. Thus, this study shows that MDRD and MDPvD formulae for GFR calculation underestimates the value by 60 to 90 mL / min / 1.73 m^2 in young hypertensive patients with a short history of the disease.

The results of our study (Table 3) showed a lower accuracy of GFR calculated by CKD-EPI formula in comparison with the Cokcroft-Gault. The difference between the GFR calculated by Cokcroft Gault formula and the Rehberg reference method was only 0.6% (that is, there was no difference), however, the CKD-EPI express formula showed a difference of 10.0% ($p < 0.025$) (Table 3).

From the foregoing it therefore follows that the routine application of the formulae for the calculation of GFR (MDRD, MDPvD, CKD-EPI is not suitable for accurate determination of the filtration function of the kidneys in the entire population and in patients with a long history of kidney disease. On the selected limited group of young people with no pathology of the kidneys, it is definitely shown that the glomerular filtration rate calculated by the MDRD, MDPvD, CKD-EPI formulas does not reflect (i.e. underestimates) the functional state of the kidneys. It is therefore necessary to avoid MDRD, MDPvD, CKD-EPI formulae in conditions when accurate assessment of GFR in healthy individuals and patients with a short history of hypertension (without kidney disease). Instead, express calculation by Cokcroft Gault or Rehberg method should be performed. However, the Cokcroft-Gault formula has been observed to have some shortcomings [4, 8]. This formula does not fully reflect GFR in persons with malnutrition, in vegetarians, in patients with amputated limbs, in immobilized individual – for example, in spinal cord injuries. The inaccuracy of the result is also likely to occur in cases of abnormal fat metabolism, in those with hypertrophied somatic muscles, excessive consumption of meat or food additives with creatine, as well as in persons with labile renal function and in elderly patients. The Cokcroft-Gault formula, however, is used in routine practice to date [2, 4]. In particular, it remains the method of choice for the calculation of GFR when deciding on the dosage of the drugs to be administered, as well as in the diagnosis of kidney damage in hypertension [1, 3, 8].

The Rehberg method of GFR calculation uses only the level of endogenous creatinine – refers to the clearance express method and has the advantage of ease of implementation, since it does not require intravenous administration of the test substance [2]. Evaluation of GFR based on measurement of plasma creatinine levels and urine creatinine with consideration of the calculated minute urine output for many years was generally accepted. As shown by the results of this study, GFR, determined by the Rehberg method was 126.8 ± 5.43 ml / min, and when standardized to 1.73 m^2 – 105.7 ± 3.6 ml / min / 1.73 m^2. The disadvantage of the Rehberg test is, first of all, due to the inaccuracy of the result in the late stages of renal failure, when creatinine begins to be secreted in the renal tubules [4, 8]. An additional inconvenience to the patient is the need to collect urine during the day. Disorder of the rules of collecting urine often leads to an erroneous result [2, 4, 8]. But in healthy people or patients without renal failure to accurately determine GFR, the Rehberg method remains relevant [2, 4].

Various methods of evaluating GFR have been developed [1, 2, 4, 8, 9], and reference methods include clearance methods using exogenous substances. In this way, renal filtration is assessed by the inulin elimination rate, ^{51}Cr-EDTA, ^{125}I-iotalamate or yogexol. The introduction of these methods into routine clinical practice is limited by their complexity, the need for intravenous administration of foreign substances, as well as high cost involved. Therefore the calculation methods which have been shown to be effective in assessing renal functions are routinely used in clinical setting.

5 Conclusion

The mean values of GFR by Rehberg and by Cokcroft Gault do not have significant differences – both at baseline ($p > 0.05$) and when standardized to 1.73 m^2 ($p > 0.05$). The GFR value obtained by the calculation method using the MDRD formula is significantly lower than the standardized result according to Rehberg ($p < 0.001$) and Cokcroft-Gault ($p < 0.001$). The GFR value obtained by the express calculation method using MDPvD (ml / min / 1.73 m^2) is significantly lower than the standardized result according to Rehberg ($p < 0.001$) and Cokcroft Gault ($p < 0.001$). The value of GFR obtained by the calculation method using the CKD-EPI (ml / min / 1.73 m^2) is significantly lower than the standardized result according to Rehberg ($p < 0.05$) and Cokcroft-Gault ($p < 0.025$). For accurate assessment of GFR in healthy individuals and patients with a short history of hypertension (without kidney pathology), it is best to avoid using MDRD, MDPvD, CKD-EPI formulae and use either express calculation by Cokcroft-Gault or Rehberg method.

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