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Two-Hour Creatinine Clearance and Glomerular Filtration Rate Estimated from Serum Cystatin C and Creatinine in the Elderly to Preoperative Period

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ABSTRACT

Introduction: The utility of estimates of glomerular filtration rate based on creatinine and cystatin C serum levels to assess renal function in older surgical patients remains to be determined. **Objective:** To determine whether 2h-creatinine clearance (CrCl-2h) can be an adequate substitute for glomerular filtration rate estimates obtained by measuring serum cystatin C and creatinine in the elderly at preoperation. **Methods:** A total of 102 consecutive elder patients undergoing pre-anesthesia evaluation for routine surgeries were included. Study subjects were allocated into three groups: Group 1 (G1)—hypertensive diabetic patients, Group 2 (G2)—hypertensive patients, and Group 3 (G3)—non-hypertensive and non-diabetic patients. Two-hour urine collection was performed and CrCl-2h adjusted for ultrasonic residual bladder volume was estimated. GFR was estimated based on creatinine and cystatin C serum levels. Bland-Altman analysis was used to compare methods. **Results:** The mean difference between the evaluated methods and CrCl-2h was <15 mL·min^{-1}·1.73 m^{-2} for Cys-GFR, and >20 mL·min^{-1}·1.73 m^{-2} for Cr-GFR in all groups. CrCl-2h adjusted for ultrasonic residual bladder volume did not differ from non-adjusted CrCl-2h in none of the groups. **Conclusion:** Two-hour creatinine clearance was not an adequate substitute for GFR estimates based on creatinine and cystatin C serum levels in older patients at preoperation. The ultrasonic assessment of residual bladder volume had no significant influence on the calculation of two-hour creatinine clearance.

Keywords: Renal Function; Creatinine Clearance; Cystatin C; Elderly

1. Introduction

Subclinical renal disease, frequently seen in the diabetic and long-term hypertensive elderly, increases the risk associated with anesthesia and surgery, and enhances the susceptibility of these individuals to intraoperative renal failure, leading to high postoperative mortality rates [1-3].

The collection of urine output over 24 hours is one of the methods that have been used to assess renal function as it eliminates the potential error due to the existence of residual bladder volume, particularly in older people. However, a 24-h urine collection may not be feasible during preoperative evaluation delaying the availability of information for clinical evaluation [4].

In 1988, Cardenas *et al.* [5] described a small portable ultrasound device, specifically designed to determine bladder volumes that can be operated with minimal training. According to these authors, volumes estimated using this noninvasive method correlate with those obtained by urethral catheterization. Thus, the assessment of renal function at 2-h intervals using ultrasound bladder scan to eliminate the bias associated with postmicturition residual volume would be useful for the preoperative evaluation of elderly patients. Among intensive care patients, 2-h creatinine clearance has been demonstrated to be an adequate substitute for 24-h clearance, even in unstable patients [6].

Whether estimates of glomerular filtration rate based on creatinine and cystatin C serum levels are compared with 2-h creatinine clearance to assess renal function in older patients remains to be determined. Despite being an earlier marker of renal failure, cystatin C has not shown

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advantages over creatinine in the elderly [7]. Therefore, the purpose of this study was to assess whether creatinine clearance determined by a 2-hour urine collection adjusted for residual bladder volume is an adequate substitute for glomerular filtration rate estimates obtained by measuring serum cystatin C and creatinine in older patients before surgery.

2. Methods

This study was approved by the Committee of Research Ethics of Botucatu Medical School, and written informed consent was obtained from all subjects.

The study population consisted of 102 consecutive elderly patients (≥65 years) who underwent pre-anesthesia evaluation for routine orthopedic, gastrointestinal, vascular, or gynecologic surgery in a tertiary university hospital.

Study subjects were allocated into three groups: Group 1 (G1)—hypertensive diabetic patients, Group 2 (G2)—hypertensive patients, and Group 3 (G3)—non-hypertensive and non-diabetic patients. Patients were considered hypertensive and diabetic when diagnosis and specific treatment for these conditions had been established prior to admission. Patients with heart failure, renal failure requiring dialysis, anuria or kidney transplant were excluded. All patients had surgical diseases and were receiving preoperative in-patient care.

For renal function assessment, post-void residual urine volume was checked using a BVI 5000 ultrasound scanner (Diagnostic Ultrasound Corporation, USA). With the patient lying supine, the scanhead was lubricated with conductive gel (gel pad Sontac 50) and positioned approximately 5 cm above the symphysis pubis. Three scans were performed on each subject and the mean volume from these scans was used as the mean urine volume. Time count was then started. Patients were asked to complete urine collection in a special container for the next two hours. After one hour, a blood sample (15 mL) was obtained for the measurement of creatinine (mg/dL), urea (mg/dL), cystatin C (mg/L), and glycated hemoglobin (%). By the end of the two-hour interval, patients were asked to void in a container. From the total urine volume voided, a sample was collected for creatinine assessment (mg/dL). Ultrasonic residual volume was then measured again. Three readings were taken and the mean volume from these readings was added to the amount collected in the container. Adjusted urine volume was estimated by subtracting the initial residual volume from this sum. Urine output per minute ($mL \cdot min^{-1}$) was obtained by dividing the adjusted residual volume by the time elapsed to obtain it. Two-hour creatinine clearance ($mL \cdot min^{-1}$), or two-hour glomerular filtration rate (GFR), was estimated from the equation [urine creatinine (mg/dL) × adjusted two-hour urine volume (mL/min^{-1})/blood creatinine (mg/dL)].

Serum cystatin C measurements were performed by latex enhanced reagent (N Latex Cystatin C, Dade Behring, Deerfield, IL, USA) using a Behring BN ProSpec analyser (Dade Behring) and Dade Behring calibrators. The test was performed according to the in- structions of the manufacturer. Serum creatinine was measured by a dry chemistry technique at the Chemistry Laboratory of the hospital.

Creatinine-estimated GFR was calculated by the Cockcroft & Gault formula [8] where (GFR_{CG}) = [140 − age (years) × weight (kg) / 72 × blood creatinine (mg/dL) × 0.85 (if female). GFR from cystatin C was calculated by the Larsson *et al*. formula [9] where ($GFR_{Larsson}$) = [77.24 × cystatin $C^{-1.2623}$ (mg/L)]. GFR and two-hour creatinine clearance were expressed per 1.73 m^{-2} of body surface area by multiplying measured values by 1.73 of body surface area. Anthropometric data, such as age (years), gender, weight (kg), height (m^2) and body mass index (kg/m^2) were collected during preoperative clinical evaluation.

Statistical Analysis

Sample size (n = 102) was calculated to detect a difference of at least 15% between GFR by serum creatinine and two-hour creatinine clearance. Assuming a probability of 5% for a type I error and 20% for a type II error, 34 patients in each group would allow two-tailed comparisons. Median and 25% - 75% percentiles were used as a measure of central tendency and variability due to non-normal distribution of the study data. Categorical variables were reported as absolute values and percentages. Comparisons were performed with the non-parametric Kruskal Wallis test for continuous variables, followed by the a posteriori Dunn test for multiple comparisons if $P > 0.05$. Significance was set at $P < 0.05$. CrCl-2h adjusted for ultrasonic residual bladder volume and not adjusted CrCl-2h was compared by Mann-Whitney test.

Because analysis with correlation and least squares linear regression is fundamentally misleading, Bland and Altman analysis [10] was used to compare the differences between the methods for glomerular filtration rate measurement (Y axis) plotted against their mean (X axis). Bias was defined as the mean value of the differences between methods. If the 95% limits of agreement (mean ± 2SD) between methods were not clinically important, methods were considered interchangeable. The confidence intervals for the 95% limits of agreement were calculated by mean difference ±1.96 standard deviation of the differences. Bland and Altman analysis [10] of the GFR estimates was performed with Medcalc (Medical

Software, Mariakerke, Belgium).

3. Results

Patient median age was 71 years (65 - 88 years). Males accounted for 66.34% of the study population. In diabetic patients, median glycated hemoglobin was 7.2%.

Study groups were homogeneous according to age, gender and body mass index ($kg \cdot m^{-2}$). There was no statistically significant difference in adjusted urine volume, two-hour creatinine clearance (CrCl-2h), creatinine-estimated glomerular filtration rate (Cr-GFR) and Cystatin-C estimated GFR (Cys-GFR).

The mean differences between the evaluated methods and CrCl-2h were 3.67 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ for Cys-GFR, and 27.44 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ for Cr-GFR in **G1**; 2.29 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ for Cys-GFR and 22.96 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ for Cr-GFR in **G2;** 13.10 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ for Cys-GFR and 40.40 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ for CR-GFR in **G3** (**Figure 1**). Limits of agreement between Cys-GFR - CrCl-2h and Cr-GFR - CrCl-2h were showed in **Table 1**.

CrCl-2h adjusted for ultrasonic residual bladder volume did not differ from non-adjusted CrCl-2h in all patients (**Figure 2**).

4. Discussion

The assessment of renal function using creatinine concentration as a marker has several limitations in the elderly. Two hour-creatinine clearance would then be an important alternative for assessing renal function serially and at short intervals.

In this study, CrCl-2h was compared with glomerular filtration rate and estimates from creatinine and cystatin C. Our data showed that CrCl-2h better agreed with cystatin C-estimated GFR (Larsson equation) than with creatinine-estimated GFR (Cockcroft & Gault equation) in older patients. The mean difference between the evaluated methods and CrCl-2h was < 15 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ for Cys-GFR, and >20 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ for Cr-GFR in all groups. A mean difference between methods of 18 -

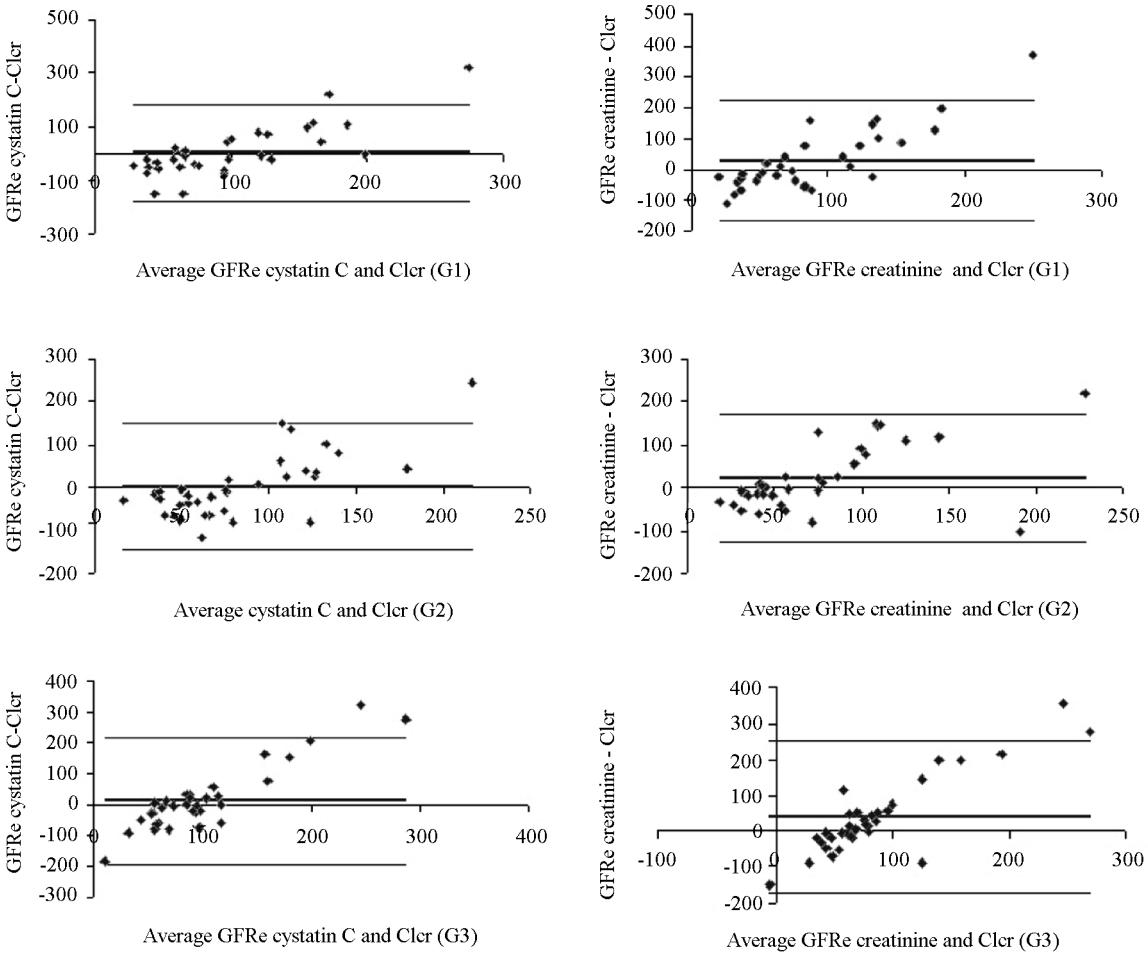

Figure 1. Bland-Altman plot for differences between Cys-GFR, Cr-GFR and two-hour creatinine clearance (CrCl-2h) per group (G1-G3) in the preoperative period. Horizontal lines indicate the mean reflecting the mean difference and the span between +1.96 SD and −1.96 SD of the mean difference between CrCl-2h and the methods evaluated (Cys-GFR and Cr-GFR).

Table 1. Bland-Altman for differences between Cys-GFR, Cr-GFR and two-hour creatinine clearance (CrCl-2h) per group (G1-G3) in the preoperative period. Limits of agreement - Upper limit (+1.96 SD) (CI 95%) and lower limit (−1.96 SD) (CI 95%) (mL·min^{-1}·1.73 m^{-2}).

Limits of agreement	Groups		
Cystatin C-GFR*	**G1**	**G2**	**G3**
Upper limit (CI 95%)	187.50 (131.02; 144.03)	149.58 (99.74; 190.26)	218.60 (155.46; 281.75)
Lower Limit (CI 95%)	−180.26 (−236.77; −126.76)	−145.00 (−194.55; −104.33)	−192.40 (−255.54; −129.26)
Creatinine-GFR*			
Upper limit (CI 95%)	220.73 (161.35; 280.14)	171.62 (125.96; 217.33)	250.51 (183.65; 315.89)
Lower Limit (CI 95%)	−165.85 (−225.25; −106.46)	−125.80 (−171.4; −80.03)	−169.71 (−239.70 ; −107.47)

*mL·min^{-1}·1.73 m^{-2}.

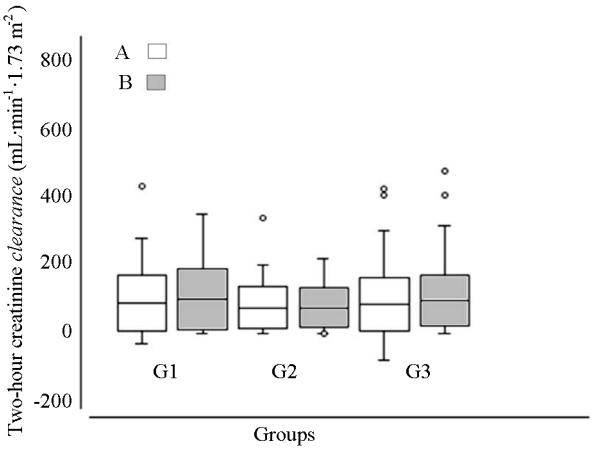

Figure 2. Comparison of CrCl-2h adjusted (B) and not adjusted (A) for ultrasonic residual bladder volume (mL·min^{-1}·1.73 m^{-2}) in elder patients during the preoperative period. Box plots - Bars represent median values, boxes represent interquartile ranges, and whishers show 95% confidence intervals. Mann-Whitney Test: A = B in G1, G3 and G3.

20 mL·min^{-1}·1.73 m^{-2} [6] was considered acceptable. However, although CrCl-2h values showed a better agreement with Cys-GFR, the wide limits of agreement between these methods, which reflect the great variation of the results obtained, did not allow concluding that these methods actually agree and can be used interchangeably.

In intensive care patients, Gutierrez *et al.* [6] found a close correlation between 24-h and 2-h creatinine clearance that remained even with the use of diuretics or in the presence of low or irregular diuresis, suggesting that such methods are interchangeable. These authors further report that 24-h creatinine clearance correlated poorly with GFR estimated by the Cockcroft & Gault equation.

Diabetes and hypertension, which have the kidney as a target organ, tend to worsen renal function in older patients. The diabetic and hypertensive elderly included in this study was receiving preoperative care for routine surgery, and was, therefore, well compensated. Moreover, those who were diabetic had satisfactory previous glycemia control as measured by glycated hemoglobin. This fact may explain why no difference in preoperative renal function was detected among groups.

Studies comparing cystatin C with creatinine measurements have produced conflicting results. While some have demonstrated that cystatin C is more sensitive than creatinine in detecting renal failure [11-13], others have reported no difference between these markers [7,14]. This disparity is likely to be due to differences in study population. In patients with normal or slightly reduced renal function, cystatin C seems to be superior to creatinine. In contrast, in patients with a marked decline in renal function, differences between cystatin C and creatinine are smaller as frequently observed in older patients [11,14].

Because the formula of Cockcroft & Gault may overestimate renal function when GFR >60 mL·min^{-1}·1.73 m^{-2}, cystatin C is clearly more useful in these cases. In this study, in which individuals with markedly reduced renal function were not included and most elderly patients showed GFR >60 mL·min^{-1}·1.73 m^{-2}, cystatin C was a more adequate marker of renal function than CrCl-2h [15]. The Cockcroft & Gault formula might have overestimated GFR, and this would explain the increased difference between mean CrCl-2h and mean Cockcroft & Gault formula values seen in our older patients. However, other studies have demonstrated that cystatin C has no advantages over creatinine in population with GFR < 60 mL·min^{-1}·1.73 m^{-2} [14]. Thus, the severity of pre-existing renal disease should be considered when selecting the method to be used for the assessment of renal function in older patients.

The use of ultrasound to measure residual bladder volume in order to obtain more precise two-hour urine volume estimates is essential in the elderly. In this population, physiological disorders such as prostatic hypoplasia and bladder prolapse can lead to underestimation of the two-hour volume measured. Nonetheless, whether adjusted or not for residual bladder volume, CrCl-2h values did not differ among our patients. An explanation for this

finding is that few residual amounts cannot be easily detected by ultrasound examination and this might have influenced the interpretation of the results.

Diurnal variation in diuresis is another factor that has been suggested to interfere with CrCl-2h assessment. However, creatinine clearance estimates obtained at a shorter interval (8 hours) have been demonstrated to be as accurate as 24-h clearances [16].

In conclusion, two-hour creatinine clearance was not an adequate substitute for GFR estimates based on creatinine and cystatin C serum levels in older patients at preoperative period. The ultrasonic assessment of residual bladder volume had no significant influence on the calculation of two-hour creatinine clearance.

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