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Plasmatic cystatin C for the estimation of glomerular filtration rate in intensive care units

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Abstract *Objective:* To compare the sensitivity of cystatin C and creatinine in detecting decreased glomerular filtration rate. *Design:* Prospective observational study. *Setting:* Medical intensive care unit at a university hospital. *Patients and participants:* Fourteen patients hospitalised in a medical intensive care unit. *Interventions:* Cystatin C and creatinine plasmatic levels were measured in 40 blood samples taken with an interval of at least 24 h. *Measurements and results:* Glomerular filtration rate was estimated by creatinine clearance using 24-h urine collection and the classical Cockcroft-Gault equation. The ability of cystatin C to detect a glomerular filtration rate under 80 ml/min per 1.73 m^2 was significantly better than that of creatinine ($p<0.05$). *Conclusions:* Cystatin C, a new plasmatic marker of renal function, could be used to detect renal failure in intensive care in the future.

Keywords: creatinine ; critical care ; cystatin C ; glomerular filtration rate ; Kidney function tests

Introduction

Serum creatinine, the classic serum marker used for renal function evaluation, frequently overestimates the glomerular filtration rate (GFR) [1]. Recently, a new GFR plasmatic marker has been studied: cystatin C [2]. Freely and totally filtrated at glomerular level, cystatin C is fully metabolised by proximal tubular cells. Therefore, the urinary level of cystatin C is very low in healthy patients. In cases of tubular injury, the urinary level of cystatin C increases but the plasmatic level of cystatin C increases only when it is associated with a decrease in glomerular filtration [3]. Neither inflammation nor proliferative diseases can influence its plasmatic level, which is completely independent of muscular mass [4, 5, 6]. A rise in the cystatin C plasmatic level only occurs in cases of GFR decrease [7] and, perhaps, in cases of corticotherapy or thyroid dysfunction [8, 9]. To our knowledge, cystatin C has never been evaluated in intensive care patients. In this study, we compare cystatin C with creatinine in order to determine which of the two markers is the more sensitive in detecting renal failure.

Methods

Population

Fourteen patients hospitalised in our intensive care unit were included in this study. Cystatin measurement was performed on 40 blood samples taken routinely for creatinine measurement with an interval of at least 24 h between samples. Patients were in a stable haemodynamic status, were not treated with corticoids and had no profound thyroid dysfunction. All the patients had a urinary catheter and none required renal replacement therapy.

Measurements

Serum creatinine was measured by the classic Jaffé reaction. The reference for serum creatinine in our laboratory ranges from 9 to 13 mg/l for men and from 7 to 10 mg/l for women. Cystatin C was measured by immunonephelometric technology (PENIA for "particle-enhanced nephelometric immunoassay")[10]. The reference for cystatin C is, as published by Galteau et al.: 0.48-0.82 mg/l for women under 50 years, 0.54-0.94 mg/1 for men under 50 years and 0.63-1.03 mg/l for patients over 50 years [11]. The GFR was estimated using two methods: measurement of creatinine clearance using 24-h urine collection (corrected for the body surface area index [BSA]) and the classical Cockcroft-Gault equation, also corrected for BSA [12]. Actual body weight was used in the Cockcroft-Gault formula. In our study, a GFR above 80 ml/min per 1.73 m^2 was considered to be normal.

Statistical analysis

Renal function evaluation methods were compared by correlation analysis and the receiver operating characteristic (ROC) curves method. Reference values for GFR were creatinine clearance measured by 24-h urine collection and calculation by the Cockcroft-Gault formula. The areas under ROC curves were calculated

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for each parameter and compared.

Chi-square test was used to compare false negative percentage of reduced GFR obtained from creatinine and cystatin C values. Data are expressed as means ± standard error of the mean (SEM). A *p* value less than 0.05 was considered statistically significant.

Results

The study included ten men and four women (63±4 years old). The mean BMI and BSA were 26.08±6.68 kg/m^2 and 1.86±0.21 m^2, respectively. The mean SAPS score was 42±4. All patients were mechanically ventilated and haemodynamically stable with only one patient on vasopressors. The underlying disease was stroke (*n*=1), intestinal bleeding (*n*=2), endocarditis (*n*=1), subarach-noid haemorrhage (*n*=1), pneumonia (*n*=3), lymphoma (*n*=1), epilepsy (*n*=2), acute pulmonary oedema (*n*=1), myocarditis (*n*=1) and cardiac arrest (*n*=1). One to eight measurements (2.9±0.4) per patient were performed.

The GFR estimated by 24-h creatinine clearance was less than 80 ml/min per 1.73 m^2 in 31 measurements out of 40 (77.5%) and the GFR estimated by the Cockcroft-Gault formula was less than 80 ml/min per 1.73 m^2 in 29 measurements out of 40 (72.5%). With both methods, 11 patients had GFR under 80 ml/min per 1.73 m^2. No patient with normal GFR developed renal failure.

We found a significant correlation between 1/creatinine and the GFR, estimated either by creatinine clearance (*r*=0.4) or by the Cockcroft-Gault formula (*r*=0.88) (Fig. 1). With 1/cystatin C, the correlation coefficient was 0.68 for GFR estimated by creatinine clearance and 0.85 for GFR estimated by the Cockcroft-Gault formula (Fig. 2). There was no difference between correlations for 1/creatinine or 1/cystatin C if GFR estimated by the Cockcroft-Gault formula was used as a reference (*p*=0.095). However, if GFR estimated by creatinine clearance was used as a reference, we found a statistically better correlation for 1/cystatin C than for 1/creatinine (*p*=0.005).

Fig. 1 *Correlation between 1/creatinine and glomerular filtration rate estimated by creatinine clearance obtained from Cockcroft-Gault equation*

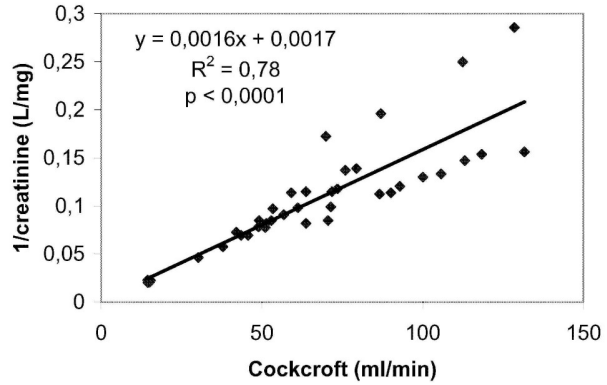
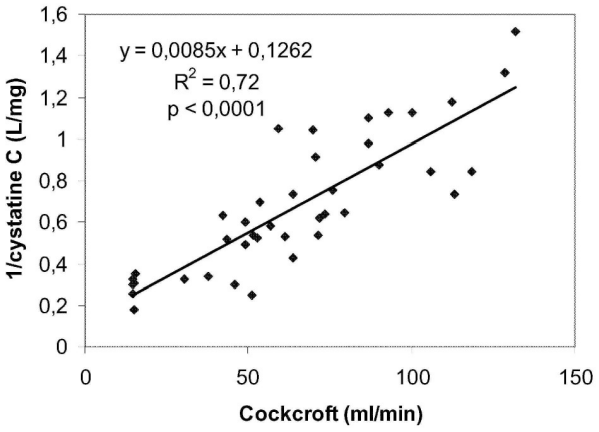


Fig. 2 *Correlation between 1/cystatin C and glomerular filtration rate estimated by creatinine clearance obtained from Cockcroft-Gault equation*



The area under the curve was greater for cystatin C (area of 0.833 with GFR estimated by creatinine clearance

and 0.918 with GFR estimated by the Cockcroft-Gault formula) than for creatinine (0.789 with GFR estimated by creatinine clearance and 0.882 with GFR estimated by the Cockcroft-Gault formula). However, this difference was not statistically significant (p=0.54) (Figs. 3 and 4).

Serum creatinine values were in the normal range, although the GFR was under 80 ml/min per 1.73 m^2 in 42% of the cases when GFR estimated by creatinine clearance was used and in 38% of the cases when GFR estimated by the Cockcroft-Gault formula was used. If published references for cystatin C were considered, a false negative rate of only 16% was calculated when GFR estimated by creatinine clearance was used and of only 7% when GFR estimated by the Cockcroft-Gault formula was used. The ability of cystatin C to detect a GFR under 80 ml/min per 1.73 m^2 was significantly better than that of creatinine (p<0.05).

Fig. 3 *Receiver operating characteristic curves for creatinine (closed squares) and cystatin C (open squares) if glomerular filtration rate estimated by Cockcroft-Gault equation is used as reference*

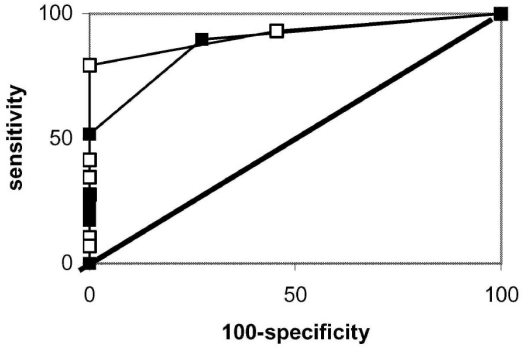
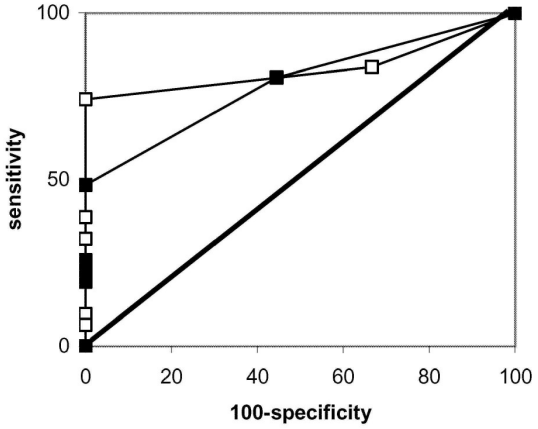


Fig. 4 *Receiver operating characteristic curves for creatinine (closed squares) and cystatin C (open squares) if glomerular filtration rate estimated by measurement of creatinine clearance with 24-hour urine collection is used as reference*



Discussion

In this study we showed, for the first time, that plasma cystatin C was more sensitive than serum creatinine in detecting renal failure in intensive care patients.

Patients in intensive care frequently present decreased muscular mass. Therefore serum creatinine, which depends on the muscular protein creatine, may remain abnormally low and thus overestimate true GFR [1, 12, 13]. The increased sensitivity of plasma cystatin C can be explained by this phenomenon as cystatin C concentration is independent of lean tissue mass [6, 7].

Measurement of inulin clearance is the gold standard technique used to estimate GFR [12, 13]. Other methods have been specifically studied in intensive care: amino-glycoside, 99mTc-DTPA and iohexol clearances [14, 15, 16]. However, all these techniques are very difficult to apply, expensive and uncommon in clinical practice [12, 14].

Practically GFR was therefore estimated either by the classic Cockcroft-Gault formula or by the creatinine clearance calculated from 24- or 2-h urine collection [17, 18]. Using inulin clearance as the GFR reference, Erley

et al. showed that 24-h creatinine clearance resulted in a more accurate prediction of GFR than the Cockcroft-Gault formula [14]. By contrast, Robert et al. showed that the Cockcroft-Gault equation resulted in a more accurate prediction of GFR than urine creatinine clearance measures [19]. Thus, in our study, differences in correlation coefficients between cystatin C and GFR estimated by the Cockcroft-Gault formula, on the one hand, and GFR estimated by creatinine clearance, on the other hand, are not surprising. This emphasises the need to confirm our results with a more accurate method of GFR measurement.

The ability of cystatin C to detect a low GFR was better than serum creatinine. If moderate renal failure occurs, cystatin C values will be abnormally high more frequently than creatinine levels. Clinicians will be informed earlier and subsequently take the usual precautions to manage patients who develop renal failure in intensive care (hydration, drug dosage adaptation, etc.) [20].

This new plasmatic marker could be used in the future to detect renal failure in intensive care. Other studies with a bigger sample of patients and more accurate methods for GFR measurements (i.e. inulin or iohexol clearances) still seem necessary to confirm the utility of plasma cystatin C for the estimation of GFR in intensive care.

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