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Utility of Cystatin C for Assessment of Renal Function after Cardiac Surgery

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Key Words
Cystatin C · Acute renal failure · Glomerular filtration rate · Cardiac surgery

Abstract
Background: Though acute renal failure among cardiac surgery patients is associated with increased mortality, diagnosis of renal failure is often delayed due to the late detectability of laboratory markers for kidney failure. Recently, a number of clinical studies have shown that glomerular filtration rate (GFR) can be estimated by measuring the serum concentration of cystatin C (CysC). However, comparisons between the diagnostic effectiveness of CysC and serum creatinine have been inconsistent. The present study compares the diagnostic effectiveness of both serum markers in cardiac surgery patients. ***Methods:*** In 50 cardiac surgery patients, GFR was quantified by measuring creatinine clearance and estimated from serum concentrations of both creatinine and CysC. The sensitivity and specificity of serum creatinine and CysC for detection of reduced GFR values were compared as well as correlation between estimated GFR values and creatinine clearance. ***Results:*** GFR values <60 ml/min/1.73 m^2 were detected with equal effectiveness using creatinine or CysC, whereas for the detection of GFR <90 ml/min/1.73 m^2 the area under the curve of serum creatinine was significantly higher. Correlation between estimated GFR values and creatinine clearance was higher when creatinine-based formulae were used. ***Conclusion:*** In patients after cardiac surgery, CysC is not superior to serum creatinine for assessment of GFR.

Introduction

Acute renal failure is a common complication following cardiac surgery and has a large impact on postoperative outcome. Mortality increases dramatically when acute renal failure occurs [1, 2], and the duration of ICU care and hospitalization also increase [3, 4]. Continuous hemofiltration or hemodialysis can provide efficient detoxification and fluid management for patients, but reducing mortality may depend on minimizing the interval between the initiation of renal failure and commencement of these therapies [5, 6]. Because commencing renal replacement therapy as early as possible may have a positive influence on patient outcomes, more sensitive parameters for detecting early stage renal failure are needed.

To assess glomerular and tubular function, several laboratory tests can be used. The time requirement, cost, and diagnostic significance of available methods vary, thus choosing suitable parameters to assess renal function depends on the specific clinical situation. Creatinine clearance reflects glomerular filtration rate (GFR) with a

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fair degree of accuracy, but because urine collection over several hours is necessary, this method does not allow instantaneous estimation of glomerular function. In contrast, GFR can be calculated immediately from serum creatinine and biometric data (e.g. using the Cockroft-Gault formula), but this method results in lower precision than measuring creatinine clearance. Finally, the application of exogenous, partly radioactive indicators allows the most accurate measurement of GFR, but requires large amounts of effort [7, 8].

The protease inhibitor cystatin C (CysC) is synthesized in all nucleated cells at an age-independent, constant rate. Renal elimination of CysC involves free glomerular filtration followed by complete tubular resorption and intracellular degradation. The serum concentration of CysC depends primarily on glomerular filtration and is therefore suitable for estimating GFR [9]. In the present clinical trial, we compared serum concentrations of creatinine and CysC, thereof derived estimations of GFR and endogenous creatinine clearance. All values were measured in 50 patients, once preoperatively and every 12 h postoperatively until the bladder catheter was removed for medical reasons. The study was carried out in cardiac surgery patients for two reasons: First of all, estimation of renal function is crucial in these patients because all patients have a potential risk of acute renal failure after cardiac surgery. Secondly, it is well known that renal function varies to a remarkable extent after cardiac surgery, which allows to compare both serum markers within a wide range of GFR.

Patients and Methods

Patient Criteria

After approval by the local ethics committee and signed informed consent, 50 male patients were included in the study, which ran between December 2005 and March 2006. A preliminary test run showed that preoperative urine collection in (often bedridden) female patients was inefficient due to practical difficulties. We therefore elected to perform the study only with male patients. Other inclusion criteria were elective cardiac surgery and an age of at least 18 years. Exclusion criteria were participation in other clinical studies and the preoperative presence of terminal renal failure requiring dialysis.

Study Parameters

Assessment of renal function was done periodically by measuring serum concentrations of creatinine and CysC, estimation of GFR from both serum concentrations, and finally calculating creatinine clearance from urine samples collected simultaneously. Preoperative sampling began on the day before surgery immediately after patient consent and was ended intraoperatively before cardiopulmonary bypass was initiated. Postoperatively, the urine was collected from the bladder catheter continuously. The first sampling period started immediately after admission to the ICU, and lasted until 07:00 or 19:00 h, respectively. Blood samples were taken at the end of each sampling period. To avoid short urine collection periods (which may lead to errors in calculating creatinine clearance), the first point in time was skipped if the period between ICU admission and 07:00 h was shorter than 6 h. Subsequently, urine samples and laboratory tests (creatinine and CysC) were taken every 12 h for the entire ICU stay. For each sampling period, creatinine clearance was calculated, and GFR was estimated from serum concentrations of creatinine and CysC. According to the literature, we used the following formulae: $GFR = 175 \cdot S_{crea}^{-1.154} \cdot age^{-0.203}$ [10] and $GFR = 84.69 \cdot CysC^{-1.680}$ [11] (GFR, ml/min/1.73 m^2; S_{crea}, mg/dl, age, years; CysC, mg/l). Data of all sampling periods were subjected to statistical analysis, provided that all parameters of the particular period were available. Participation in the study was terminated when the urine catheter was removed for medical reasons.

Measurement of Laboratory Values

Serum and urine creatinine concentrations were measured enzymatically (IDMS-traceable) in the central laboratory of the University Hospital of Göttingen immediately after collection of the specimens. CysC measurements from single blood specimens were performed by the Department of Nephrology, University Hospital of Göttingen on a Dade-Behring BN2 analyzer (Dade-Behring, Marburg, Germany) using the Dade-Behring N Latex Cystatin C assay, which is a particle-enhanced nephelometric immunoassay for serum CysC levels. The assay time was 6 min, the sample volume was 40 μl and the measurement range was 0.23–8.10 mg/l [12]. To avoid intra-assay variance, all specimens were measured in a single batch after termination of the clinical trial. Therefore, serum from all blood samples was isolated immediately after blood withdrawal by centrifugation and stored at –30°C.

Statistical Analysis

After testing for normal distribution, differences between pre- and postoperative means of serum creatinine, CysC, estimated GFR values and creatinine clearance were calculated using t tests.

Inverse, indirectly proportional relationships between serum creatinine or CysC levels and creatinine clearance were expected (1/serum creatinine or 1/CysC ≈ creatinine clearance). Thus, correlation coefficients between reciprocal values of serum creatinine or CysC and creatinine clearance were calculated.

ROC analyses were performed to analyze the ability of serum creatinine and CysC to detect a reduced GFR. According to the guidelines of the National Kidney Foundation, cutoff points of GFR were set at <90 ml/min/1.73 m^2 ('slightly low') and <60 ml/min/1.73 m^2 ('moderately low') [13]. Finally, we calculated the correlation coefficients between creatinine clearance and estimated GFR values from serum creatinine and CysC, respectively. Calculation of correlation coefficients and t tests were performed using Statistica 6.1 software (StatSoft, Tulsa, Okla., USA), Accumetric 1.1 (Accumetric Corp., Montreal, Canada) was used for ROC analyses.

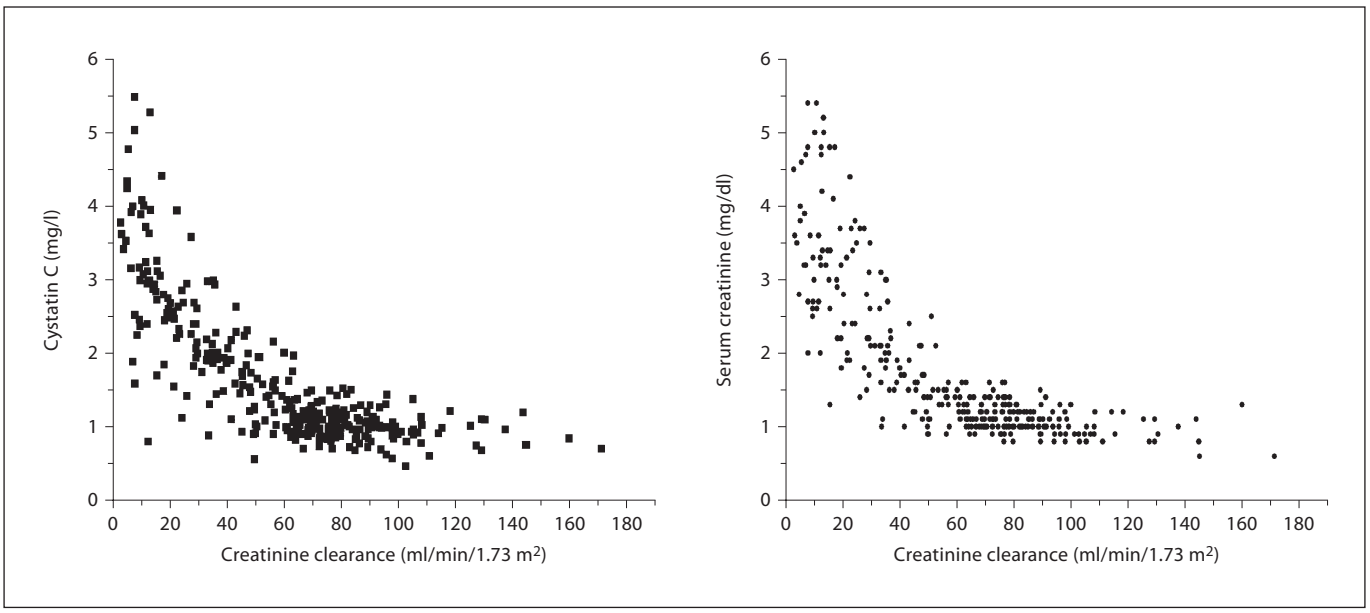

Fig. 1. Serum concentrations of creatinine (right) and CysC (left) plotted against creatinine clearance values.

Table 1. Biometric data and preoperative renal function parameters

	Age, years	Height, cm	Weight, kg
Mean ± SD	67.0 ± 9	174.0 ± 6	85.0 ± 13
Range	47.0–83.0	157.0–186.0	65.0–122.0

Results

Biometric Data, Surgical Procedures and Sampling Periods

Biometric data are summarized in table 1. Patients were admitted for aorto-coronary bypass (60%), aorto-coronary bypass combined with aortic valve replacement (18%), isolated aortic valve replacement (12%), aortic surgery with cardiopulmonary bypass (6%) and mitral valve surgery (4%). A total of 323 collection periods (including creatinine clearance, serum concentrations of creatinine and CysC and resulting GFR estimations) were completed. Depending on the duration of urine catheterization, the number of collection periods per patient ranged from 3 to 22 (median 6).

Pre- and Postoperative Renal Function Parameters

Comparison of the pre- and postoperative means of renal function parameters showed a significant increase for both serum markers creatinine and CysC. Accordingly, the means of estimated GFR values as well as endogenous creatinine clearance were decreased postoperatively. Except for GFR estimated from serum CysC, all changes were statistically significant (table 2).

Figure 1 shows the relationships of serum creatinine and CysC to creatinine clearance. Both graphs have the same hyperbolic shape, indicating an inverse, indirectly proportional correlation between serum concentrations and creatinine clearance.

To evaluate the correlation between the serum parameters and creatinine clearance, reciprocal values of serum creatinine and CysC were plotted against creatinine clearance (fig. 2). Correlation coefficients were calculated to compare these linear relationships. We found that the correlation coefficient between creatinine clearance and 1/serum creatinine was significantly higher than that between creatinine clearance and 1/CysC (0.841 vs. 0.759, $p = 0.0035$).

Additionally, ROC analyses were performed to assess the ability of serum creatinine and CysC to detect limited GFR values <90 or <60 ml/min/1.73 m^2. For the detection of creatinine clearance values <90 ml/min/1.73 m^2, serum creatinine was superior to CysC ($p = 0.0497$),

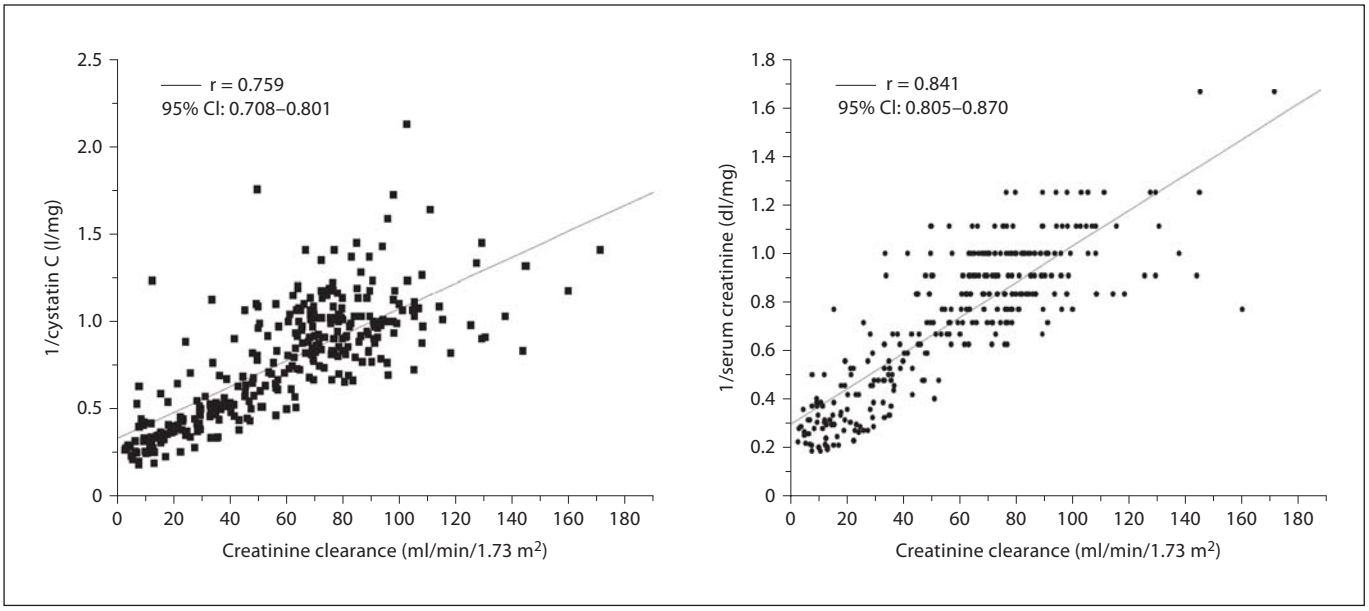

Fig. 2. Correlation between creatinine clearance and 1/serum creatinine (right) and 1/CysC (left).

Table 2. Pre- and postoperative renal function parameters

Parameter	Mean (95% CI)		p value
	preoperatively	postoperatively	
Serum creatinine, mg/dl	1.12 (1.04–1.20)	1.59 (1.50–1.69)	<0.001
Serum cystatin C, mg/l	1.07 (0.98–1.18)	1.51 (1.42–1.60)	0.001
Creatinine clearance, ml/min/1.73 m^2	58.1 (50.6–66.7)	45.6 (41.3–50.5)	<0.001
GFR estimated from S_{crea}, ml/min/1.73 m^2	68.4 (63.4–73.4)	50.7 (47.7–53.7)	0.003
GFR estimated from CysC, ml/min/1.73 m^2	85.0 (74.6–95.4)	57.4 (52.2–62.3)	0.241

whereas the diagnostic accuracy of both parameters was similar at a cutoff point of 60 ml/min/1.73 m^2 (fig. 3).

Finally, we calculated GFR values from serum concentrations of creatinine and CysC. The correlation coefficients between GFR values derived from both serum markers, and corresponding creatinine clearance values were calculated and compared (fig. 4). The correlation coefficient between creatinine clearance and GFR estimated from serum creatinine was significantly higher than between creatinine clearance and GFR estimated from serum CysC (0.849 vs. 0.703, p = 0.0035). In figure 5, the comparison between GFR values derived from serum creatinine and CysC related to endogenous urinary creatinine clearance is shown as a Bland-Altmann plot.

Discussion

Clinical trials that investigate new measures of renal function are important for ICU medicine because currently available tests have important limitations. Measurements using exogenous indicators require large amounts of effort and cannot be performed in every laboratory. Estimating serum creatinine allows for easy and instant assessment of GFR and is thus very commonly used, but due to the 'creatinine blind' range of GFR the ability of this test to detect moderately reduced GFR values is relatively poor. Measurement of endogenous creatinine clearance reflects GFR much more closely, but the required urine collection is time-consuming and is a potential source of errors. Additionally, high serum creati-

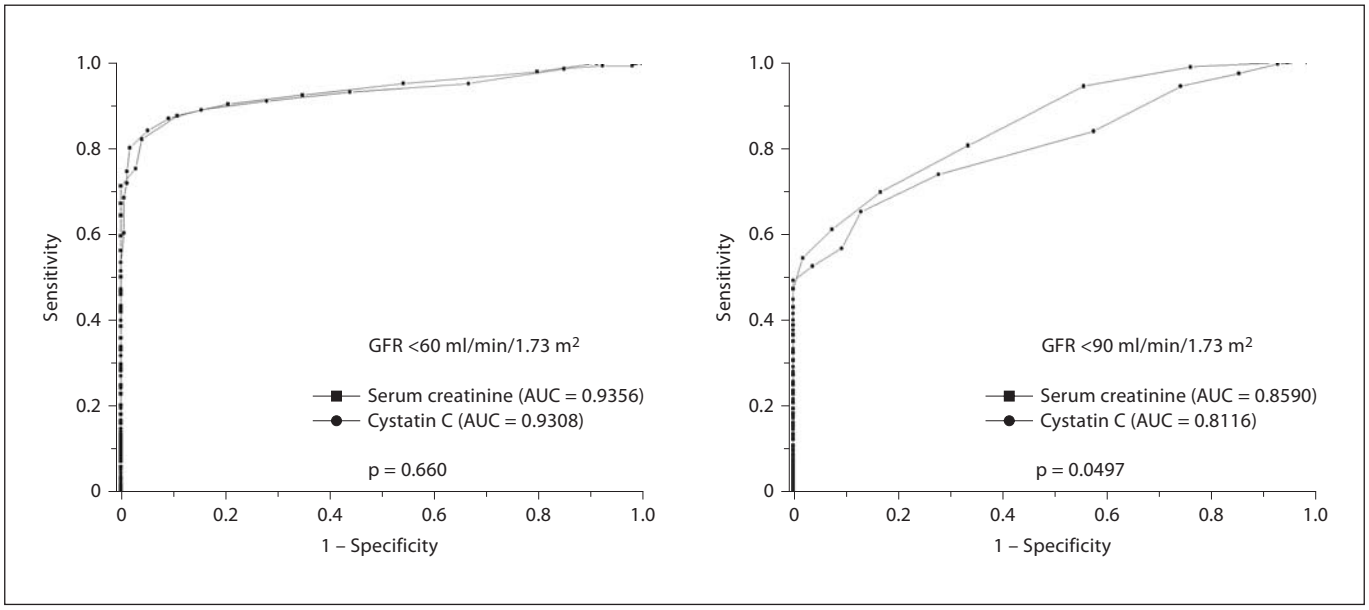

Fig. 3. ROC curves of serum creatinine and CysC for the detection of a GFR <90 ml/min/1.73 m^2 (right) and <60 ml/min/1.73 m^2 (left).

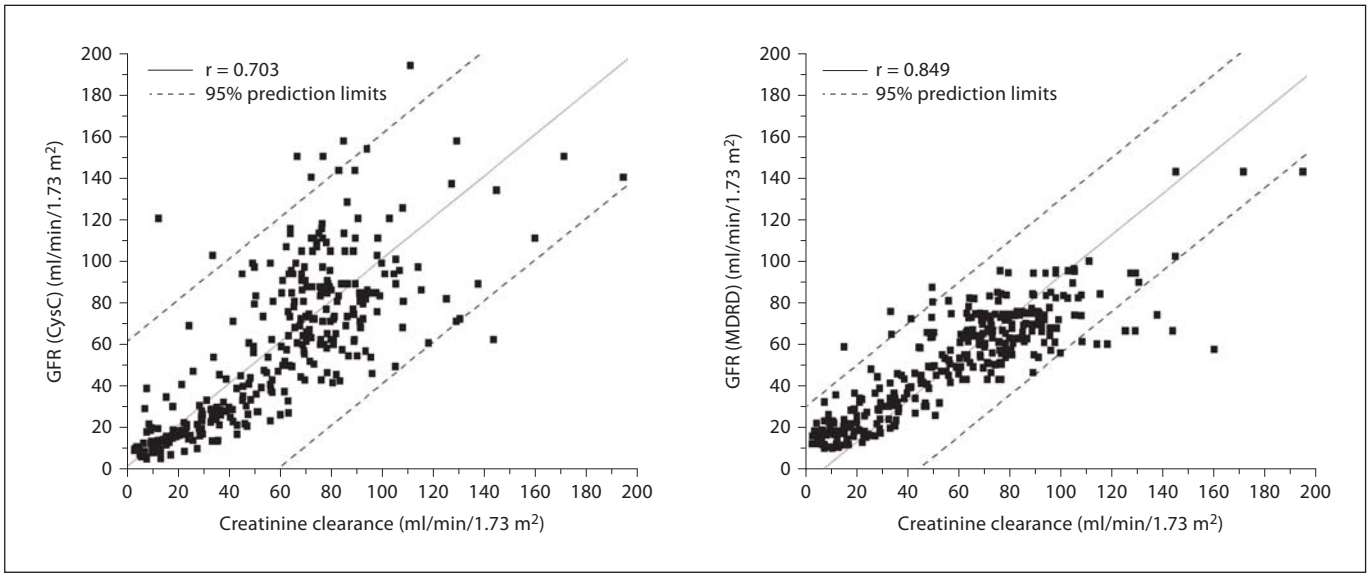

Fig. 4. Correlation between creatinine clearance and GFR values estimated from serum creatinine (right) and CysC (left).

nine levels can cause increased tubular secretion and lead to higher urine creatinine levels, resulting in overestimation of GFR.

To compare the diagnostic value of both serum parameters CysC and creatinine within a wide range of GFR (based on endogenous creatinine clearance), the study was carried out in cardiac surgery patients in whom renal function can vary to a remarkable extent.

Many studies have compared the diagnostic accuracy of serum creatinine and CysC in non-cardiac surgery pa-

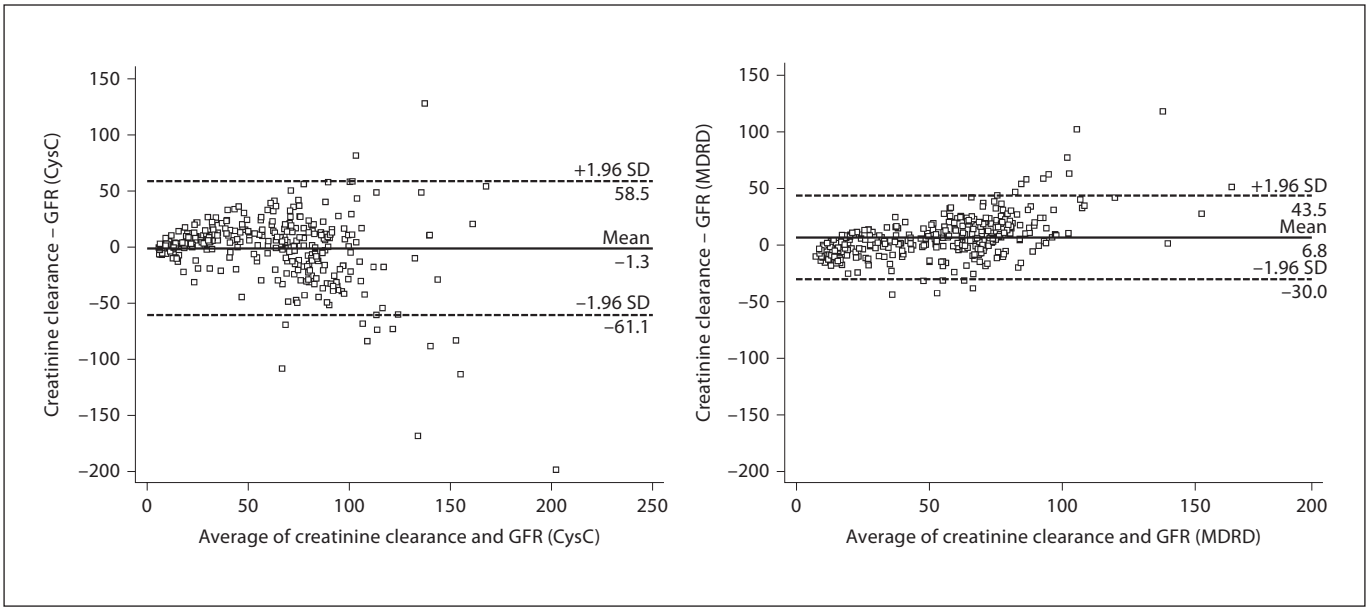

Fig. 5. Comparison of creatinine clearance and GFR values estimated from serum creatinine (right) and CysC (left) as Bland-Altmann plots.

tients before, but the results have been inconsistent: in line with our results, several studies did not show any advantage of CysC measurements over serum creatinine measurements [14–17]. In contrast, other clinical trials have concluded that CysC is more sensitive for the detection of impaired GFR, at least when compared with serum creatinine [18–20].

To explain this apparent discrepancy, it is important to note that creatinine and CysC are eliminated by similar mechanisms. Both are filtered freely in the glomeruli and eliminated completely (creatinine by excretion with urine, CysC by tubular resorption and intracellular degradation). Serum concentrations of both markers hence are predominantly determined by GFR, and the hyperbolic shape of their correlation curves confirms that serum creatinine and CysC concentrations are indirectly inversely proportional to the GFR [14, 21]. Figure 2 clearly shows that the reciprocal relationships between serum concentrations of creatinine and CysC and GFR are reflected in our results. Taken together, these results strongly suggest that the biochemical properties of these markers do not recommend one over the other for the assessment of glomerular function, especially when GFR is only slightly impaired. In fact, analogous to the creatinine blind range for a moderately reduced GFR, a 'cystatin blind' range also seems to exist in which changes of GFR do not cause significant changes in CysC serum concentration (fig. 1, 3). The diversity of these results might be explained by the fact that extrarenal factors can influence serum concentrations of creatinine and CysC independently of the GFR. For example, cimetidine reduces the tubular secretion of creatinine and thus interferes with creatinine-based measurements of GFR; likewise, heavy exercise, muscular damage or excessive consumption of meat can change creatinine levels [22]. Serum concentrations of CysC are also influenced by extrarenal factors [23]. Two studies have reported significant changes in CysC levels after correcting for hypo- and hyperthyroidism, respectively [24, 25]. The idea that these changes in CysC were independent of GFR is supported by the finding that serum creatinine levels changed in the opposite manner in these studies. Another extrarenal factor influencing CysC levels is the application of high doses of corticosteroids, which can increase CysC levels under clinical conditions [26, 27]. Both of these mechanisms potentially play considerable roles in cardiosurgery patients: hypothyroidism is a well-known problem in ICU medicine ('low T_3 syndrome' [28]), and high doses of steroids are often applied in an attempt to reduce systemic inflammation responses to cardiopulmonary bypass surgery. Inconsistency in the ability to detect reduced GFR in different patient groups might be due to extrarenal factors that influence serum creatinine or CysC, leading to putative differences in their diagnostic values.

Although on the whole, published data suggests that serum creatinine and CysC are equivalently useful for the assessment of glomerular function (at least in the absence of specific extrarenal disturbances), there seems to be an interesting difference in their chronological course: Herget-Rosenthal et al. [29] examined 85 patients with elevated risk of acute renal failure and showed that significant increases in CysC levels appeared 24–48 h before changes in creatinine levels were detectable.

Limitations of the study may result from the fact that GFR was calculated from the urinary clearance of endogenous creatinine. Though GFR can be measured with a much better accuracy by clearances of exogenous markers (such as iohexol or radioactive labeled substances), these methods were ineligible due to their high amount of efforts. On the other hand, the most important reasons leading to the inaccuracy of urinary creatinine clearance are incomplete bladder emptying and inaccurate adherence to urine collection times. These problems were eliminated by sampling the urine continuously via bladder catheter. Under these circumstances, urinary clearance of endogenous creatinine seemed to be an acceptable compromise between accuracy and feasibility for calculating GFR, as other clinical studies showed in ICU patients and even after short urine collection periods [30, 31].

Conclusion

Measuring CysC levels is as effective as measuring serum creatinine for detection of mild changes in urinary clearance of endogenous creatinine. In agreement with several clinical studies, our results did not show that measuring CysC was superior to measuring creatinine. In contrast to these findings, other clinical trials have found measurement of CysC to be superior to measurement of serum creatinine. Since the mechanisms of renal filtration are the same for creatinine and CysC, these differences are likely caused by extrarenal factors that influence serum levels of only one marker and cause selective inaccuracies in GFR estimates. Measuring CysC levels is reliable for estimating GFR if extrarenal influences like thyroid hormone imbalance or application of large doses of steroids can be excluded.

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