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Determination of Glomerular Filtration Rate After Contrast-Enhanced CT Among Critically Ill Patients: Support for a New Procedure

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OBJECTIVES: To measure glomerular filtration rate using iohexol plasma clearance ($mGFR_{iohexol}$) in critically ill patients using the high doses of iohexol administered at CT and to evaluate its agreements with urinary creatinine clearance (uCl_{cr}) and estimated glomerular filtration rates (eGFRs), calculated from plasma concentrations of creatinine ($eGFR_{cr}$) and cystatin C ($eGFR_{cys}$).

DESIGN: Prospective observational cohort study.

SETTING: ICUs across Southeast Sweden.

PATIENTS: Critically ill adult patients.

INTERVENTIONS AND MEASUREMENTS: Twenty-six ICU patients were given high doses of iohexol (range, 27–140 mL) for contrast-enhanced CT, whereafter blood samples were taken in the elimination phase for determination of $mGFR_{iohexol}$. Plasma iohexol concentrations were determined by high-performance liquid chromatography and $mGFR_{iohexol}$ was calculated. Standard dose (5 mL) of iohexol was administered the following days to compare low-dose clearance results with the high-dose clearance results. Six-hour uCl_{cr} was performed four times a day and averaged.

MAIN RESULTS: Mean ± SD $mGFR_{iohexol}$ after CT was 77.4 ± 38.1 mL/min (n = 26), and uCl_{cr} was 97.3 ± 58.2 mL/min (n = 25) in the critically ill patients. There was a strong positive correlation between $mGFR_{iohexol}$ determined with high and low doses of iohexol in patients with normal or high $mGFR_{iohexol}$ (coefficient of determination [R^2] = 0.88; $p < 0.001$) and between $mGFR_{iohexol}$ and uCl_{cr} (R^2 = 0.87; $p < 0.001$). $eGFR_{cr}$ overestimated $mGFR_{iohexol}$ and $eGFR_{cys}$ underestimated $mGFR_{iohexol}$.

CONCLUSIONS: $mGFR_{iohexol}$ after contrast-enhanced CT compares well with $mGFR_{iohexol}$ after standard low-dose iohexol respectively uCl_{cr}. Over- and underestimation of $mGFR_{iohexol}$ by $eGFR_{cr}$ and $eGFR_{cys}$ is probably explained by increased tubular secretion of creatinine and increased production of cystatin C in intensive care patients.

KEYWORDS: computed tomography; glomerular filtration rate; high-dose iohexol plasma clearance; intensive care unit patients

When dosing renally excreted drugs, the patient's glomerular filtration rate (GFR) should be considered. Current estimated GFR (eGFR) methods, which are based on plasma creatinine and cystatin C, are too uncertain to be relied upon in patients requiring intensive care (1, 2).

Measured glomerular filtration rate using iohexol plasma clearance ($mGFR_{iohexol}$) has been the reference method (gold standard) for the determination of GFR in many European countries and is gaining interest in the United

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KEY POINTS

Question: Can iohexol from contrast-enhanced CT of critically ill patients be used for determination of measured glomerular filtration rate using iohexol plasma clearance ($mGFR_{iohexol}$), and how does this high-dose $mGFR_{iohexol}$ correspond to urinary creatinine clearance (uCl_{cr}) and estimated glomerular filtration rates (eGFRs) from plasma creatinine ($eGFR_{cr}$) and cystatin C ($eGFR_{cys}$)?

Findings: This clinical cohort study showed that high-dose $mGFR_{iohexol}$ correlated well with uCl_{cr}. $eGFR_{cr}$ was significantly higher and $eGFR_{cys}$ was significantly lower than $mGFR_{iohexol}$.

Meaning: Measuring plasma iohexol from CT makes accurate GFR determinations rapidly available for the intensive care patients and diminishes problems with assessments of $eGFR_{cr}$ and $eGFR_{cys}$.

States (3). Typically, 5 mL of a concentrated solution of iohexol is administered as an IV bolus, and plasma clearance is calculated from timed plasma concentrations following the distribution phase after the injection. This procedure is safe for the patients (1, 3–5). Although clinically useful, this low-dose $mGFR_{iohexol}$ is seldom used as support for drug dosing in patients admitted to ICUs. The method is considered complicated, takes time to implement, and requires accurate information on the amount of injected iohexol as well as an exact time schedule for blood sampling (1, 3, 6). A laboratory that can measure the iohexol concentrations with a short response time must also be available.

The pharmacokinetics of iohexol is independent of dose as shown several years ago in healthy subjects (7–9). Recently, Gong et al (10) showed that administration of 50 mL of iohexol gave the same clearance rates as the standard dose of 5 mL in healthy subjects.

Our pilot study on critically ill patients showed that determining GFR was feasible after administration of high-dose iohexol during CT (11). This proof of concept was confirmed in a study of 27 critically ill patients (12). With well-organized routines, it is possible to have plasma iohexol concentrations analyzed and $mGFR_{iohexol}$ calculation done within the day.

The aim of the present study was to investigate if high-dose $mGFR_{iohexol}$ after contrast-enhanced CT could be used for determination of GFR in ICU patients. Simultaneously, we wanted to evaluate how urinary creatinine clearance (uCl_{cr}) and eGFRs, calculated from plasma concentrations of creatinine ($eGFR_{cr}$) and cystatin C ($eGFR_{cys}$), aligned with $mGFR_{iohexol}$.

MATERIALS AND METHODS

Study Design

The Swedish Ethical Review Authority approved the study (Reference No. 2020-04197, "Användning av iohexol tillfört vid röntgenundersökning för beräkning av glomerulär filtration hos Intensivvårdspatienter," approved October 7, 2020). Informed consent was obtained from the patients, or in the case of an unconscious patient, a family representative was informed in accordance with Swedish law. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975.

Patients were recruited from one neurosurgical ICU and two general ICUs in Southeast Sweden. Patients were included as determined by the patients' physicians if they were older than 18 years old and if there was no competing activity. Pregnancy and ongoing renal replacement therapy were exclusion criteria.

The primary study design was to measure the high-dose $GFR_{iohexol}$ clearance after CT and validate the results by assessing low-dose iohexol clearance (gold standard) performed the day after the high-dose iohexol. On the study day, a pretest of iohexol concentration was collected before the patients were referred to the x-ray departments, using 4 mL serum collecting tubes with coagulation activator added. We used serum for the analysis of iohexol as an adequate substitute for plasma. Thereafter, iohexol (350 mg iodine/mL = 755 mg iohexol/mL; GE Healthcare AB, Danderyd, Sweden) was administered IV at the doses required for the CT. The median iohexol dose was 80 mL (range, 27–140 mL). This corresponds to a median of 18.7-fold (range, 6.3–32.7) higher than the amount given in the standard $mGFR_{iohexol}$ procedure with 5 mL. The exact injection time and dose were noted. After the return to the ICU, four blood samples were collected using the same type of serum collecting tubes as in the pretest, sampled at 3, 4, 5, and 6 hours at the scheduled time frames according to Bröchner-Mortensen (13) and Bröchner-Mortensen and Rödbro

(14). The $eGFR_{cr}$ and $eGFR_{cys}$ results from the previous day were used for the preliminary assessment of this time frame. Standard clearance investigations were performed on the following day using 5 mL Omnipaque (300 mg iodine/mL = 647 mg iohexol/mL). On each occasion, five blood samples were collected for analysis. However, when implementing the study, the protocol had to be revised due to nature of the patient's different conditions and course at the ICU. As a result, in several patients the low-dose iohexol was administered more than one day after the high-dose iohexol. In addition, among patients with reduced renal function, too much iohexol remained in plasma, invalidating the calculation of the standard low-dose iohexol investigation on day 2.

Laboratory Measurements

Blood samples collected for analysis of iohexol were centrifuged and serum was stored at −70°C pending analysis. Serum concentrations of iohexol were determined using a slightly modified reversed-phase high-performance liquid chromatography (HPLC) method, based on the protocol reported by Gaspari et al (15). To deproteinize the serum samples, four volumes of 3.5 mol/L perchloric acid containing 0.33 mol/L Isopaque cysto (as an internal standard) (Takeda Pharma, Stockholm, Sweden) were added. After 15 minutes, the samples were centrifuged at 10,000*g* for 4 minutes.

Twenty microliters of the resulting supernatant were injected into a Waters Alliance HPLC system (Milford, MA) equipped with a Waters Photodiode Array Detector (Milford, MA) set at 254 nm and a 125 × 4 mm column packed with LiChrosorb C-18 (Merck, Darmstadt, Germany). Iohexol was eluted using a mixture of 20 mmol/L citrate buffer and acetonitrile (95:5 by volume) at a flow rate of 1.0 mL/min. Internal calibration curves (linear up to 800 µg/mL) were prepared for each set of samples. Among the first samples taken after the CT dose, the highest plasma concentration (3000 µg/mL) was obtained in a patient given 140 mL of iohexol. Samples from the CTs with concentrations higher than 500 µg/mL were diluted 1:10 with a serum pool free of iohexol, before analysis.

Controls at three concentration levels (35, 100, and 600 µg/mL) were included in each analytical run. The high-concentration control was diluted 1:10 with a serum pool free of iohexol and analyzed both undiluted and diluted to ensure the reliability of the results for high-concentration samples. Between-series variation was 5% across all levels, and the lower limit of quantification was established at 2 mg/L.

Plasma cystatin C and creatinine levels were determined at local laboratories in Linköping, Växjö, and Kalmar. The laboratories used Cobas instruments (Cobas C 501/701, Cobas 6000, and Cobas Pro/Pure) from Roche (Roche Diagnostics, Mannheim, Germany). The method for cystatin C was a particle-enhanced turbidimetric immunoassay standardized against the ERM-DA471/IFCC reference material. The method for creatinine was an enzyme method standardized against isotope dilution mass spectrometry-traceable reference method (16). All three laboratories participate in the Equalis external control system for cystatin C and creatinine.

Measured and Estimated Clearances

The Bröchner-Mortensen (13) method was used to calculate iohexol clearance. This method presumes that for normal and slightly reduced clearances, clearance should be calculated from samples taken 180–300 minutes after injection, and at low clearance from samples taken 600 minutes and forward. Another prerequisite is that no iohexol should be present in the sample obtained before injection. In cases where a point was not in line with the other three points, clearance was calculated from the remaining three concentrations. To obtain the values indexed to body surface area (BSA), the absolute clearance values (mL/min) were multiplied by the factor 1.73/BSA, where BSA calculated according to Dubois and Dubois (17).

$eGFR_{cys}$ (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI], cys, 2012) was calculated according to the equation given by Inker et al (18), $eGFR_{cr}$ (CKD-EPI crea, 2021), and the combined $eGFR_{cr}$ and $eGFR_{cys}$ ($eGFR_{cr, cys}$; CKD-EPI, crea, cyst, 2021) were calculated according to the creatinine- and cystatin C-based equations to estimate GFR without race (19). We checked all estimates using the calculator at https://www.kidney.org/professionals/kdoqi/gfr_calculator. These eGFR data are given as indexed values in mL/min/1.73 m^2 and to calculate the individual subjects' absolute eGFRs (mL/min), we multiplied the indexed values by the factor BSA/1.73 m^2.

We also calculated accuracy, defined as the degree to which the result of a measurement, calculation, or specification conforms to the correct value of a standard. We compared the estimations of GFR from plasma creatinine and cystatin C with that of $mGFR_{iohexol}$.

Urine was collected four times a day in 6-hour portions. uCl_{cr} was calculated using the formula: $Cl = \frac{U \times V \times 1000}{P\text{-creatinine} \times T}$, where U is the urine creatinine concentration in mmol/L, V is the urine volume in mL, P-creatinine is the plasma creatinine concentration in μmol/L, and T is the time in minutes. We then calculated the mean values over 24 hours from the four different collections. If one or more of the four urine portions were missing, we used the available ones.

Statistics

Statistical analyses were performed using the Statistical Package for Social Sciences (Version 29.0.2.0 software; IBM Corp., Armonk, NY). Descriptive statistics for continuous variables are expressed as mean values ± SD. Standard analyses included a one-sample *t* test and linear regression for parametric continuous variables. A two-tailed *p* value of less than 0.05 was considered statistically significant.

Linear regression was used to determine the linear dependence between eGFRs and $mGFR_{iohexol}$ (Pearson correlation). The agreement between the reference method and eGFRs was also visualized by difference plots. One-sample *t* test was used to compare the mean difference between different variables in mL/min/1.73 m^2. Continuous variables were calculated as mean and SD. To compare eGFRs with $mGFR_{iohexol}$, we used the Bland-Altman procedures (20–22).

RESULTS

In total, 26 critically ill ICU patients, ten women and 16 men, with a mean age of 59 ± 15 years were enrolled. The causes of admission to the ICU were heterogeneous and were related to, for example, different conditions in the brain, sepsis, pneumonia, and organ failure (**Table 1**). Renal function varied greatly.

Absolute $mGFR_{iohexol}$ after the high-dose iohexol could be determined for all patients independently of renal function and ranged from 14 to 152 mL/min (**Fig. 1*A***). The indexed $mGFR_{iohexol}$ ranged from 15 to 113 mL/min/1.73 m^2 (**Fig. 1*B***). The mean ± SD absolute and indexed $mGFR_{iohexol}$ were 77.4 ± 38.1 mL/min and 66.0 ± 27.5 mL/min/1.73 m^2, respectively. Six patients with normal or high $mGFR_{iohexol}$ levels could be evaluated with the standard 5 mL low-dose $mGFR_{iohexol}$, three of them with repeated investigations. Two patients were investigated day 3 and day 4, one patient day 4 and day 5, and one patient day 8, all results similar to the high-dose iohexol $mGFR_{iohexol}$ (**Fig. 2**). High-dose $mGFR_{iohexol}$ after contrast-enhanced CT showed a strong positive correlation with the standard $mGFR_{iohexol}$ (R^2 = 0.88; $p < 0.001$). In patients with decreased renal function, a substantial iohexol concentration from the high-dose iohexol remained in plasma day 2, which precluded exact calculation of $mGFR_{iohexol}$ from the low-dose iohexol injection.

Two hundred twenty-five 6-hour urine samples were collected to determine uCl_{cr} over a maximum of 3 days. Ninety-nine samples were collected on day 1. A full set of four 6-hour samples was obtained from 22 patients, three 6-hour samples from three patients, and one 6-hour sample from two patients. Data were missing for one patient. In absolute terms, uCl_{cr} showed a strong positive correlation with $mGFR_{iohexol}$ from contrast-enhanced CT (R^2 = 0.87; $p < 0.001$) (**Fig. 3*A***), whereas the correlation was slightly weaker with the indexed clearance (R^2 = 0.81; $p < 0.001$) (**Fig. 3*B***). Of note is that four patients had augmented renal clearance (clearance > 130 mL/min/1.73 m^2) judged from uCl_{cr}, but none based on $mGFR_{iohexol}$ (Fig. 3*B*).

The correlations between $eGFR_{cr}$ and $mGFR_{iohexol}$ in absolute and indexed units are shown in **Figure S1** (https://links.lww.com/CCX/B511). Expressed either way, there were significant correlations between $eGFR_{cr}$ and $mGFR_{iohexol}$ ($p < 0.001$), and not unexpectedly, the R^2 values were higher with the absolute values (R^2 = 0.61 and R^2 = 0.49, respectively). It should also be noted that the correlation between $eGFR_{cr}$ and $mGFR_{iohexol}$ (Fig. 1S*A*, https://links.lww.com/CCX/B511) was less than between uCl_{cr} and $mGFR_{iohexol}$ (Fig. 3*A*; R^2 = 0.61 and R = 0.87, respectively).

When comparing $eGFR_{cys}$ and $eGFR_{cr, cys}$ to $mGFR_{iohexol}$, the former formulas showed lower or much lower clearance values than for $mGFR_{iohexol}$ (**Figs. S2** and **S3**, https://links.lww.com/CCX/B511). The correlations between absolute and indexed estimates were rather similar and statistically significant ($p < 0.001$) but with low R^2 values (R^2 = 0.36 and R^2 = 0.37) for the correlations between $eGFR_{cys}$ and $mGFR_{iohexol}$, respectively (Fig. S2, https://links.lww.com/CCX/B511) and

TABLE 1.
Demographic and Clinical Characteristics of the Patients

Patient No.	Sex	Age (yr)	Height (cm)	Weight (kg)	Plasma Creatinine (μmol/L)	Plasma Cystatin C (mg/L)	Diagnosis
1	Female	53	160	55.9	47	0.71	SAH
2	Female	62	156	79.9	45	1.14	SAH, organ failure
3	Female	57	164	64	93	1.03	Multitrauma, AKI, hypertension
4	Male	48	184	108	82	1.78	Diabetic ketoacidosis, sepsis, organ failure, hypertension
5	Male	62	187	97	130	1.22	Ileus and intestinal perforation, sepsis, organ failure, hypertension
6	Male	62	185	87	297	4.81	Pleural effusion, confusion, hypertension, sepsis, organ failure, AKI
8	Male	44	189	74.5	49	1.59	Sepsis, organ failure, pulmonary bleeding, myeloma
10	Male	25	185	154	68	1.41	Traumatic brain hemorrhage
11	Male	79	176	70.5	63	1.08	Cerebral hemorrhage
12	Male	75	175	85.5	183	2.77	Necrotizing fasciitis, organ failure, CKD
13	Female	65	171	117.1	52	0.87	SAH
14	Female	80	162	70	73	1.58	Acute subdural hematoma, diabetes
15	Male	54	178	74.5	59	0.78	Status epilepticus
16	Male	63	170	78.5	120	1.42	Pneumonia, hypotension
17	Female	79	164	61	56	1.37	Brain trauma, subdural hematoma
18	Male	32	180	71	76	0.62	Neck wound
19	Male	35	178	160.5	94	1.6	Pancreatitis, sepsis, organ failure, AKI, diabetes, hypertension
20	Male	76	181	83	66	1.1	Laryngeal edema, organ failure, diabetes, hypertension
21	Female	42	172	89.5	142	2.1	Pneumonia, AKI, sepsis, organ failure
22	Male	57	170	70	82	1	Intestinal perforation, colon cancer, sepsis, cardiac failure
23	Female	57	162	69	44	1.1	Respiratory insufficiency, pneumonia
24	Male	58	187	83	251	3.63	Sepsis
25	Female	64	156	66	170	2.42	Sepsis
26	Male	76	178	63	88	1.61	Cardiac insufficiency, ethanol intoxication, ketoacidosis
27	Female	74	165	85.5	62	1.8	Stroke, organ failure, AKI, diabetes, CKD, hypertension
28	Male	60	170	120	126	1.40	Pulmonary failure, diabetes, heart failure, hypertension, sepsis
Mean ± SD		59.2 ± 14.9	173.3 ± 10.3	86.1 ± 26.5	100.7 ± 63.8	1.61 ± 0.93	

AKI = acute kidney injury, CKD = chronic kidney disease, SAH = subarachnoid hemorrhage.

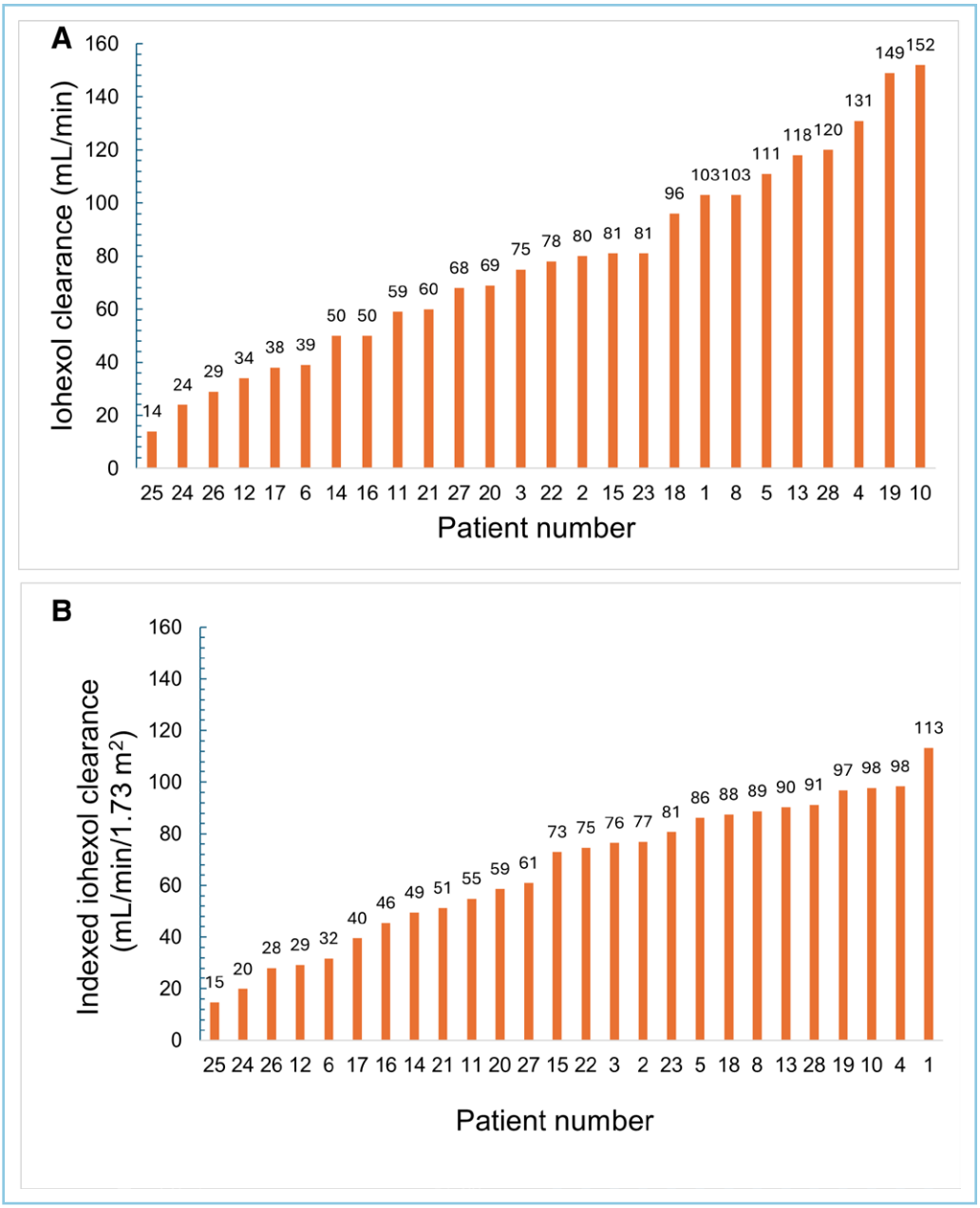

Figure 1. Iohexol clearance of the 26 ICU critically ill patients. **A**, Absolute iohexol clearance in mL/min. **B**, Indexed iohexol clearance in mL/min/1.73 m^2.

R^2 = 0.50 and R^2 = 0.46 for the correlation between $eGFR_{cr, cys}$ and $mGFR_{iohexol}$ (Fig. S3, https://links.lww.com/CCX/B511).

Figure 4 shows the differences between eGFRs and $mGFR_{iohexol}$ over the entire clearance scale in Bland-Altman diagrams. **Figure 4*A*** shows that $eGFR_{cr}$ overestimated $mGFR_{iohexol}$ by 14.23 mL/min/1.73 m^2, **Figure 4*B*** that $eGFR_{cys}$ underestimated $mGFR_{iohexol}$ by a mean of –11.74 mL/min/1.73 m^2, and that $eGFR_{cr, cys}$ gave a mean estimation close to zero compared with $mGFR_{iohexol}$. In Figures S1–S3 (https://links.lww.com/CCX/B511), the correlations, both slope and intercept, are given. **Figure 5** shows the Bland-Altman diagram of uCl_{cr} and $mGFR_{iohexol}$. The overestimation of GFR by uCl_{cr} was significant ($p < 0.001$).

DISCUSSION

Validity of High-Dose $mGFR_{iohexol}$

To the best of our knowledge, this is the first study to compare $mGFR_{iohexol}$ calculated from the high doses of iohexol administered for contrast-enhanced CT, validated by comparison with the $mGFR_{iohexol}$ determined after the standard dose (5 mL) and measured uCl_{cr} in critically ill patients. The study showed that GFR can be measured after the high doses of iohexol administered at contrast-enhanced CT, and the measured clearance compared well with the standard low dose of $mGFR_{iohexol}$ determination. Although our study is small, we consider it relevant, as others also found that high doses of iohexol have the same pharmacokinetics as low doses (7–10). The determination of $mGFR_{iohexol}$ "en passant" after high doses of iohexol for CT in critically ill patients was recently shown as a proof of concept (12). Furthermore, high-dose $mGFR_{iohexol}$ correlated well with uCl_{cr}, which also contains a component of tubular secretion. The correlation between the results obtained with high and low dosages of iohexol was strong, considering presumed variations

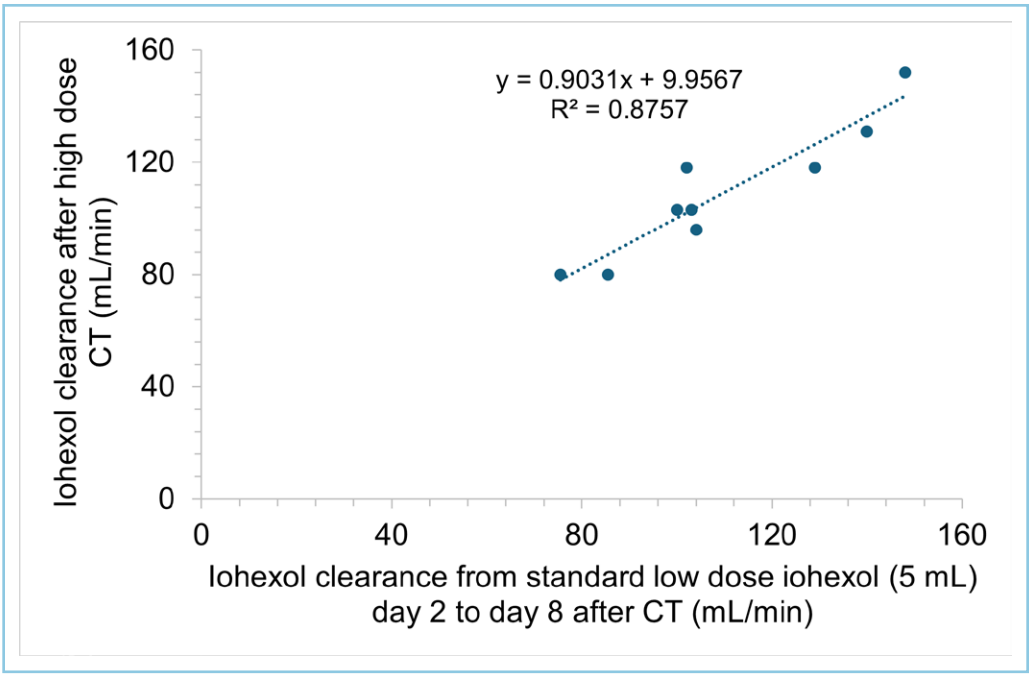

Figure 2. Correlation between measured glomerular filtration rate using iohexol plasma clearance ($mGFR_{iohexol}$) obtained from high dosage at CT with standard low-dose $mGFR_{iohexol}$.

in renal function between days. The data obtained in the patients with normal GFR clearly support dose-independent kinetics of iohexol also in critically ill patients.

Our results complement the study of Dejaco et al (12), who compared high-dose iohexol clearance with eGFRs, which are rather uncertain estimates of individual GFRs, as shown below. A clear advantage of the present study is our validation of mGFR by comparing high-dose iohexol clearance with low-dose iohexol clearance in critically ill patients.

Hu et al (9) performed renal CT angiography with 100 mL of iohexol (350 mg iodine/mL) among 19 potential living kidney transplant donors and compared the results with those obtained after a 5 mL bolus injection of iohexol (300 mg iodine/mL). Reference GFR measurements were performed approximately 2 weeks later (9). The coefficient of determination (R^2) of the index CT angiography GFR with respect to the reference standard GFR was 0.74 ($p < 0.0001$), and in our study R^2 was 0.88, which is slightly higher. Thus, our results agree with the findings in healthy subjects.

Comparison of eGFRs With $mGFR_{iohexol}$

Figure 4*C* shows that $eGFR_{cr, cys}$ was the most accurate variable, while $eGFR_{cr}$ overestimated (Fig. 4*A*), and $eGFR_{cys}$ underestimated (Fig. 4*B*) $mGFR_{iohexol}$. It has been suggested that the improved accuracy of $eGFR_{cr, cys}$ is due to each marker's compensation for the other's disadvantages (23). Our results are also consistent with the results recently published by Wang et al (24), using a cohort of 4,050 participants from 12 studies. They evaluated the accuracy of $eGFR_{cr}$, $eGFR_{cys}$, and the combination ($eGFR_{cr, cys}$) compared with mGFR according to the magnitude of the difference between $eGFR_{cr}$ and $eGFR_{cys}$ ($eGFR_{diff}$). $eGFR_{diff}$ was defined as $eGFR_{cys}$ minus $eGFR_{cr}$. In the negative $eGFR_{diff}$ groups ($eGFR_{cr} > eGFR_{cys}$), $eGFR_{cr}$ had a large overestimation of mGFR (–13.4 mL/min/1.73 m^2 [–14.5 to –12.2 mL/min/1.73 m^2]) and $eGFR_{cys}$ had a large underestimation (9.9 mL/min/1.73 m^2 [9.1–11.2 mL/min/1.73 m^2]), with opposite results in the positive $eGFR_{diff}$ group.

Implementation Into Clinical Practice

CT scans are commonly performed in ICU patients. By using valuable information about the timing and amount of injected iohexol, and by taking at least two blood samples during the elimination phase with sufficient time intervals, an accurate and precise understanding of the glomerular filtration can be obtained. A laboratory capable of urgently analyzing plasma iohexol on daily basis is necessary, particularly since critically ill patients typically have highly variable kidney function during their stay in the ICU. In a more stable ICU patient, an initial iohexol clearance after a CT scan can provide a baseline for comparison with eGFR. In addition, with population pharmacokinetic models, the number of samples can likely be minimized to one sample per day, allowing patients with low kidney function to be monitored for at least

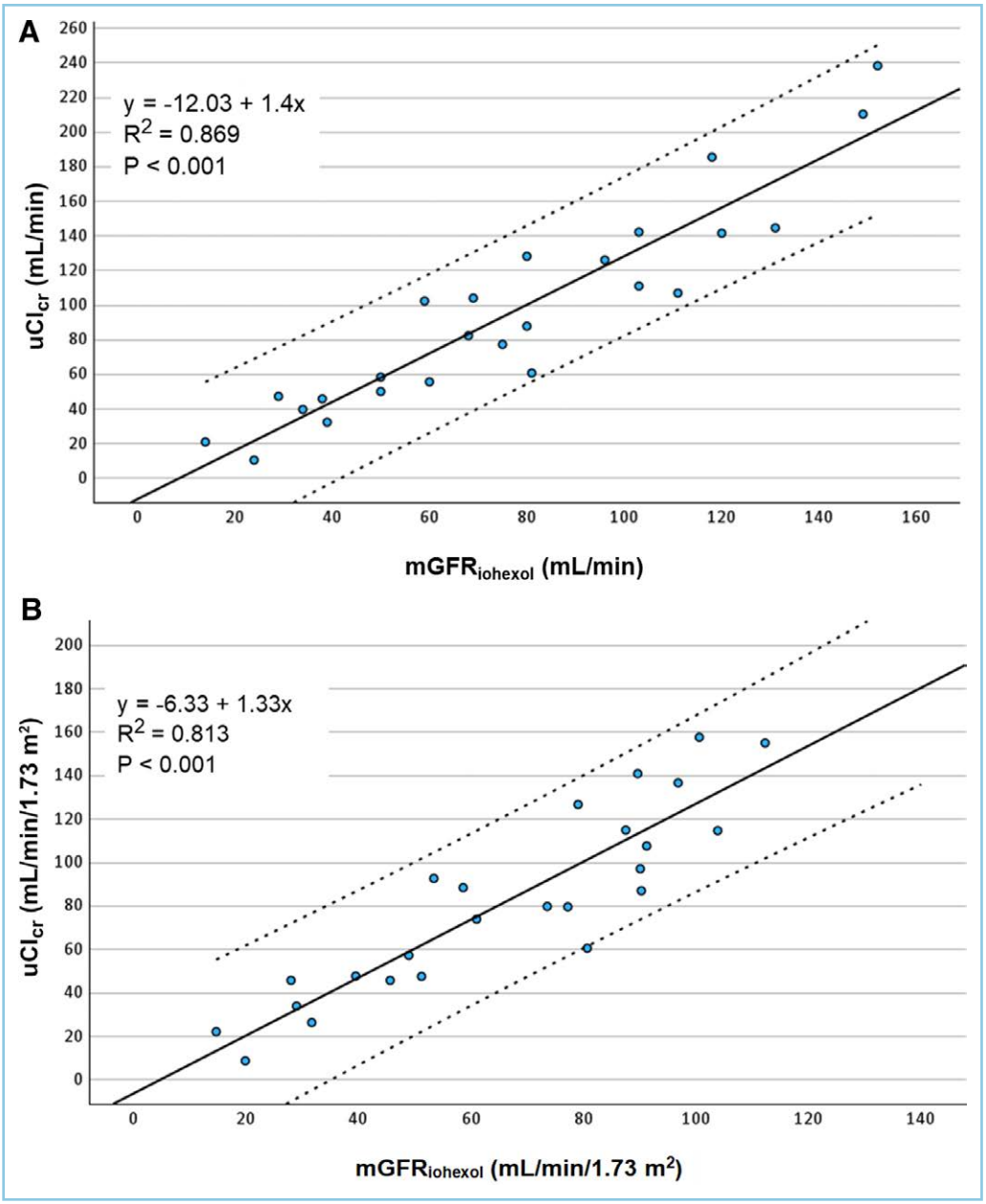

Figure 3. Correlations between urinary creatinine clearance (uCl_{cr}) and measured glomerular filtration rate using iohexol plasma clearance ($mGFR_{iohexol}$) from high iohexol dosage at CT. **A**, Absolute values. **B**, Indexed values.

2 days or more without the need for additional iohexol administration.

The calibration curve of our HPLC method used is linear up to a concentration of 800 mg/L. This means that there is a direct proportional relationship between the analyte concentration and the detector response, ensuring accurate and reliable quantification of the analyte in unknown samples. This is similar to other HPLC methods (15, 25, 26). Since the dosages of iohexol for contrast-enhanced CT are about 20-fold that of the standard method for iohexol plasma clearance, we expected the plasma concentrations also to be about 20-fold. After a first analytical run, plasma sampled with iohexol concentrations greater than 500 mg/L were therefore diluted 1:10 and reanalyzed. Such a predilution step is easily performed in hospital laboratories.

Liquid chromatography mass spectrometry (LC-MS) methods are linear up to concentration of 1500–2000 µg/mL (27, 28). Consequently, laboratories using these methods do not have to dilute the samples that much unless they want to measure the concentrations in the distribution phase for research purposes (29). Schmit et al (30) analyzed iohexol concentrations in plasma obtained from patients after iohexol injection. Bland-Altman analysis illustrated less than 1% mean bias when comparing the concentrations found with the two methods (HPLC and LC-MS) and concluded that there should be minimal bias in concentration or computed mGFR solely due to the measurement procedure employed (30). Conventional HPLC methods are generally more suitable for a 24/7 laboratory environment and are more cost-effective than LC/MS-MS methods. This is because HPLC systems are typically easier to maintain, require less specialized training, and have lower operational costs, making them ideal for continuous, round-the-clock use. The choice of analytical procedure is up to each department to decide.

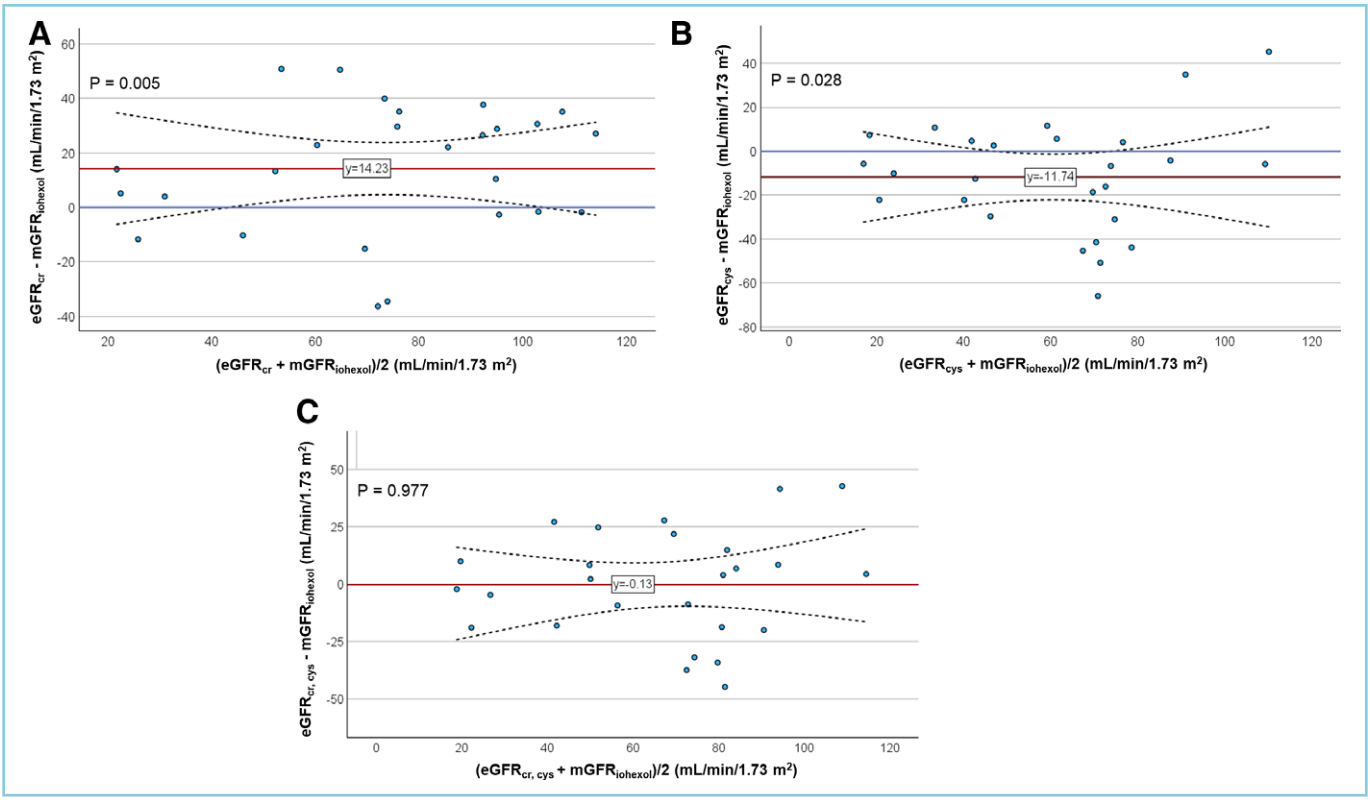

Figure 4. Bland and Altman diagrams. **A**, Estimated glomerular filtration rate from plasma creatinine ($eGFR_{cr}$)–measured glomerular filtration rate using iohexol plasma clearance ($mGFR_{iohexol}$) vs. mean of $eGFR_{cr}$ and $mGFR_{iohexol}$. **B**, Estimated glomerular filtration rate from cystatin C ($eGFR_{cys}$)–$mGFR_{iohexol}$ vs. mean of $eGFR_{cys}$ and $mGFR_{iohexol}$. **C**, Combining $eGFR_{cr}$ and $eGFR_{cys}$ ($eGFR_{cr, cys}$)–$mGFR_{iohexol}$ vs. mean of $eGFR_{cr, cys}$ and $GFR_{iohexol}$.

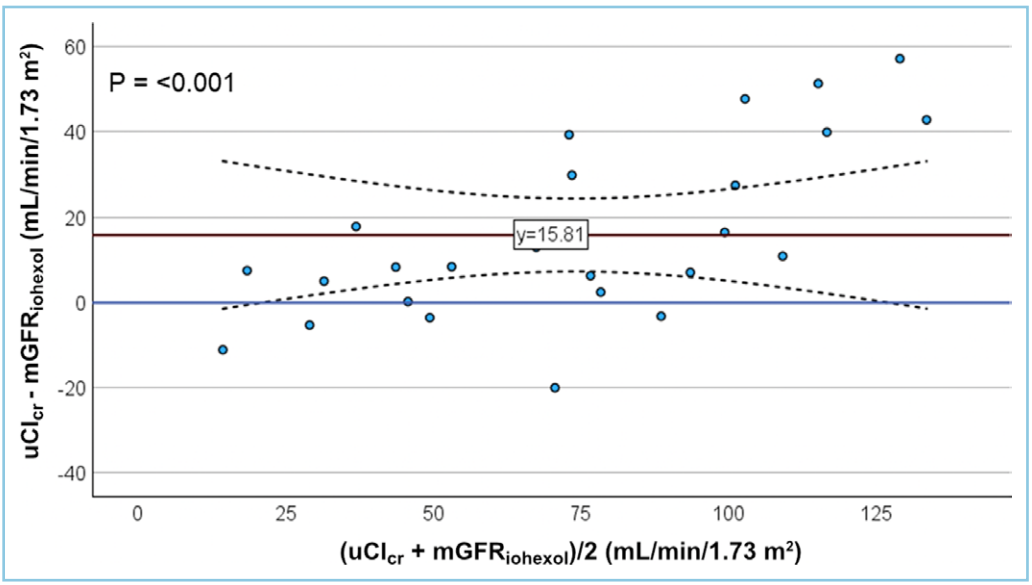

Figure 5. Bland and Altman diagram for urinary creatinine clearance (uCl_{cr})–measured glomerular filtration rate using iohexol plasma clearance ($mGFR_{iohexol}$) vs. mean of uCl_{cr} and $mGFR_{iohexol}$.

Furthermore, exchange of information between the ICU, the radiology department, and the laboratory has to be coordinated.

Finally, as shown in Figure 3, there was a tight correlation between iohexol clearance and uCl_{cr}. Based on this finding, a 6–12 hours timed uCl_{cr} is another alternative for GFR measurements in ICU patients instead of eGFR, if an iohexol method is lacking at the hospital. The handling with the urinary samples is time-consuming and laborious, requiring dedicated staff. This study showed that a few blood samples collected after iohexol contrast CT can provide reliable GFR results. We argue that this method can be implemented in hospitals with access to iohexol analysis for patients undergoing CT.

Limitations of the Study

This pilot study included 26 patients with a large age span, different diseases and conditions, and low to high renal clearance. This is a limitation, but diversity also strengthens the validity of the study. The study would have benefited from additional blood samples during the first 24 hours after CT, resulting in more complete pharmacokinetic data. Unfortunately, this was not feasible because of limited resources. Another limitation is that the comparison between $mGFR_{iohexol}$ from CT high-dose and standard low-dose iohexol could only be performed in six patients on nine occasions because of the substantial iohexol concentration remaining in plasma on day 2 in cases with low GFR. Further research on how to calculate plasma clearance when iohexol remains in the pre-sample is necessary. Another aspect is that many hospitals use other substances than iohexol for CT, for example, iodixanol. Further studies should focus on selected diagnostic categories and how other nonionic x-ray contrast media can be used as GFR markers. The wide range in plasma creatinine, both for patients with reduced and augmented renal clearance may be due to conditions for the individual ICU patient, for example, large vs. low muscle mass or brain trauma. The latter has been shown to induce augmented renal clearance (i.e., low plasma creatinine value). This emphasizes that to get a more reliable figure of renal function, a measured GFR should be obtained to a larger extent with iohexol or by measurement of creatinine clearance.

CONCLUSIONS

This study shows that $mGFR_{iohexol}$ obtained after high doses of iohexol compares well with standard low-dose $mGFR_{iohexol}$ and uCl_{cr}, confirming that the pharmacokinetics of iohexol is independent of dose. The use of analyzing iohexol concentrations after contrast-enhanced CT to measure GFR along with uCl_{cr} may be an opportunity and a good option for measuring GFR in critically ill patients. Early available results of $mGFR_{iohexol}$ and optimally timed uCl_{cr} can support adequate dosing of drugs that are eliminated by the kidneys in ICU patients.

The results also show considerable intraindividual discordance between $eGFR_{cr}$ and $eGFR_{cys}$. These biases can be corrected by using the calculated $eGFR_{cr, cys}$, but the individual variations cannot be corrected.

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