Chapter 8

Formulas Estimating Renal Function are Inaccurate and Biased in Patients with Chronic Heart Failure

Tom D.J. Smilde, Dirk J. van Veldhuisen, Gerjan Navis,

Adriaan A. Voors and Hans L. Hillege

ABSTRACT

Background Renal function is an important risk marker for morbidity and mortality in chronic heart failure (CHF). Renal function is often estimated using creatinine-based formulas. However, these formulas have never been validated in a CHF population.
Objective To validate three commonly used formulas estimating glomerular filtration rate (GFR) with true GFR in CHF patients.
Methods In 101 CHF patients (age 57±13 years, LVEF 0.28±0.10 and NYHA 2.3±0.8) we measured ^{125}I-iothalamate clearance. Cockcroft-Gault (GFR_{cg}), the Modification of Diet in Renal Disease (MDRD), and the simplified MDRD (sMDRD) equations were used as creatinine-based renal function estimations. Furthermore, 24h creatinine clearance (CrCl) was determined. The GFR, GFR_{cg} and CrCl were all corrected for body surface area (BSA). The Bland-Altman method was used to compare these formulas with the true GFR_{BSA}.
Results Mean true GFR_{BSA} was 75±27 mL/min/1.73m^2. Mean values for estimated GFR were 70±25, 67±21, 63±19 and 63±18 mL/min/1.73m^2 for $CrCl_{BSA}$, $GFR_{cg\text{-}BSA}$, MDRD and sMDRD, respectively. Mean bias was –6%, -7%, -13%, and –12% for $CrCl_{BSA}$, $GFR_{cg\text{-}BSA}$, MDRD and sMDRD. Precision (r^2) was 0.56, 0.62, 0.71, and 0.68 for $CrCl_{BSA}$, $GFR_{cg\text{-}BSA}$, MDRD and sMDRD. The 30 % accuracy (% of values within 30% of true GFR) was 81%, 76%, 83%, and 79% for $CrCl_{BSA}$, $GFR_{cg\text{-}BSA}$, MDRD and sMDRD. All formulas resulted in overestimation of the GFR in the lower ranges and underestimation in the upper ranges of the GFR_{BSA}. The predictive performance of the formulas was somewhat better in patients with severe CHF (NYHA III+IV).
Conclusions In CHF, creatinine-based formulas and $CrCl_{BSA}$ appeared to be imprecise and biased in estimating true GFR_{BSA}. Given these limitations, the MDRD is potentially the most useful formula.

INTRODUCTION

Over the last decade the prognostic and clinical value of renal function in chronic heart failure (CHF) has been generally recognised.[1;2] The "gold standard" for renal function (glomerular filtration rate: GFR) measurement is by the renal clearance of specific tracers, such as inulin or iothalamate. However, this is expensive, time-consuming and not applicable in a setting where a large number of measurements of GFR is required. Therefore, in clinical practice GFR is usually estimated by creatinine-based equations, that incorporate demographic characteristics, such as age, gender, race, and weight to account for differences in muscle mass and, hence, creatinine generation. The most commonly used formulas are the Cockcroft-Gault (GFR_{cg})[3] and the simplified Modification of Diet in Renal Disease (sMDRD) equations.[4;5] Creatinine clearance (CrCl) can also be used as a tool to measure renal function, but a 24h urine collection is required, which is inconvenient for the patient, and prone to collection failure.

The above mentioned renal function equations have been developed and validated against true GFR in populations with renal disease, where they prove to be a reasonable to good estimate of renal function.[6-8] However, in several studies in non-renal patient populations their predictive performance was disappointing.[9;10] The accuracy of these formulas varied by parameters such as gender, age and body weight, demonstrating that these formulas cannot be extrapolated to other patient populations without specific validation. Whereas several important studies in CHF estimate renal function by creatinine-based formulas, none of these formulas have been validated in CHF. There is a number of factors specific to this group of patients that may influence its accuracy and bias the formulae, such as the predominantly hemodynamic nature of the renal function impairment, medication interfering with renal function, sodium retention leading to volume expansion, and loss of muscle mass due to inactivity.

In the present study we validated in patients with CHF the predictive performance of several creatinine-based formulas estimating GFR by the "gold standard" iothalamate clearance[11;12], and analysed for the sources of bias.

METHODS

Patient population

Outpatient CHF patients, aged ≥ 18 years, LVEF < 45%, and clinically stable, were asked to participate. All patients used renin-angiotensin-system inhibitors, and all medication had been stable for at least 1 month. Exclusion criteria were a stroke or myocardial infarction within the last 3 months, cardiac surgery or angioplasty within the last 3 months or scheduled to undergo these procedures, unstable angina pectoris, primary renal disease, patients with prior organ transplant, or chronic use of renal function compromising medication. Care was taken to include patients over the full range of severity of CHF.

Study design

All patients underwent the same study protocol. On the first day, renal function was measured

by iothalamate clearance as described below.[11] Body weight and length were determined just before renal function measurement started. Two hours after the beginning of the renal measurements, venous blood was drawn to determine serum creatinine, serum urea and serum albumin. In addition, during renal measurements, blood pressure and heart rate were determined. Systolic and diastolic blood pressure measurements were calculated as the mean of the last two out of ten consecutive measurements during ten minutes in sitting position with an automatic Dinamap XL Model 9300 series device (Johnson-Johnson Medical INC, Tampa, Florida). After the renal function measurements by iothalamate were finished, patients were given two containers for two times 24h urine collection. After return of these containers, samples were taken to determine urine creatinine concentration for calculation of 24h creatinine clearance.

Renal function measurement by iothalamate clearance[11]
GFR and effective renal plasma flow (ERPF) were measured by constant infusion of radiolabelled tracers, ^{125}I-iothalamate and ^{131}I-Hippuran. After drawing a blank blood sample, a priming solution containing 0.4 ml/kg body weight of the infusion solution (0.04 MBq of ^{125}I-iothalamate and 0.03 MBq of ^{131}I-hippuran) plus an extra of 0.6 MBq of ^{125}I-iothalamate was given at 8 am, followed by infusion at 12 ml/h. In order to attain stable plasma levels of both tracers, a two hour stabilisation period followed, after which baseline measurements were started at 10 am. The clearances were calculated as (U*V)/P and (I*V)/P, respectively. U*V represents the urinary excretion of the tracer, I*V represents the infusion rate of the tracer; P represents the tracer value in plasma at the end of each clearance period. This method corrects for incomplete bladder emptying and dead space, by multiplying the urinary clearance of ^{125}I-iothalamate with the ratio of the plasma and urinary clearance of ^{131}I-Hippuran.(11,12) The filtration fraction (FF) was calculated as the ratio of GFR and ERPF and expressed as percentage. This method has a day-to-day variation coefficient of 2.5% for GFR and 5% for ERPF GFR was corrected for 1.73m^2 of body surface area (GFR_{BSA}) for comparison with the MDRD and simplified MDRD (sMDRD).

Laboratory methods
Urinary volume was measured in each collection. Serum creatinine, urea, albumin and urine creatinine were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, U.S.A.). CrCl was calculated as the mean of two 24h urine creatinine excretions divided by plasma creatinine. CrCl was also corrected for 1.73m^2 of body surface area ($CrCl_{BSA}$) for comparison with the MDRD and sMDRD. The daily creatinine production was calculated on the basis of CrCl and serum creatinine; (CrCl x screat)/70[13]. The body surface area (BSA) was determined as follows: 0.007184 x weight$^{0.425}$ x length$^{0.725}$. To obtain body mass index (BMI) weight (kg) was divided by the square of height (m^2).

Formulas estimating Glomerular Filtration Rate
Three formulas were used as creatinine-based estimations of GFR; Cockcroft-Gault, MDRD and the sMDRD. These formulas are the most commonly used formulas for estimating the GFR in CHF patients.

The Cockcroft-Gault (GFR_{cg} = mL/min) is calculated as follows[3]:
Male: ((140-age) x (weight))/72 x serum creatinine (screat).
Female: GFR_{cg} x 0.85.
BSA corrected: GFR_{cg} x (1.73/BSA) (= mL/min/1.73m^2)

The MDRD (= mL/min/1.73m^2) is calculated as follows[5]:
Male: $170 \times (screat)^{-0.999} \times (age)^{-0.176} \times (serum\ urea)^{-0.170} \times (serum\ albumin)^{+0.318}$
Black male: MDRD x1.180
Female: MDRD x 0.762
Black female: MDRD x 0.762 x 1.180

The sMDRD (= mL/min/1.73m^2) is calculated as follow[4]:
Male: $186.3 \times (screat)^{-1.154} \times (age)^{-0.203}$
Black male: sMDRD x 1.212
Female: sMDRD x 0.742
Black female: sMDRD x 1.212 x 0.742

Statistical analyses
Correlation between GFR_{BSA} and the different formulas or $CrCl_{BSA}$ were performed using Pearson's correlation coefficients. Comparison between GFR_{BSA} and the different formulas or $CrCl_{BSA}$ was performed using a paired sample T-test. A P value < 0.05 was considered as significant. The creatinine-based formulas and $CrCl_{BSA}$ were evaluated by a set of criteria to assess their predictive performance. These criteria included precision, accuracy, and bias.

Precision was evaluated by the degree of spread of series of observations and is reflected by the amount of expected variation in the estimates. The r^2 statistics were used to measure this and give an indication of the overall fit of the model.[4]

The accuracy of each equation, or how well it represents the true GFR_{BSA}, was assessed by comparing its result with those of the gold standard (iothalamate clearance). We used the following equation: [predicted value – true value (iothalamate clearance)] x 100/ iothalamate clearance.[14] For each equation, the number of subjects with predicted GFR_{BSA} values within the 15% or 30% of the iothalamate clearance was counted.

Bias is any systematic nonrandom deviation causing a prediction error and was calculated as the difference of the logarithmic transformed GFR_{BSA} and the creatinine-based formulas or $CrCl_{BSA}$. We used the antilogs to get the mean percentage deviation of the creatinine-based formulas and $CrCl_{BSA}$.[15]

The agreements between measured GFR_{BSA} and the different creatinine-based formulas or $CrCl_{BSA}$ were tested, as described by Bland and Altman.[15] The difference between measured GFR_{BSA} and creatinine-based formulas or $CrCl_{BSA}$ of each individual subject was graphed as a scatterplot with the mean of the measured GFR_{BSA} and the creatinine-based formula or $CrCl_{BSA}$ of the same individual subject. The magnitude of the differences increased in the higher ranges of GFR_{BSA}, and therefore we had to logarithmically transform the GFR_{BSA}, the creatinine-based formulas and the $CrCl_{BSA}$.[15] Scatterplots include two dotted lines representing limits of agreement (mean ± 2x standard deviation (SD). The antilog of the

mean ± 2SD is the mean percentage ± 2SD. Ninety-five percent of the differences is situated between the lines of agreement.

To identify confounding factors that could explain the observed difference between the true GFR and creatinine based formulas, we performed secondary analyses in which we determined the bias of the formulas divided within subgroups of the several parameters. Continuous variables were divided into tertiles, and per tertile the bias was calculated. The statistical analysis was performed using SPSS, Chicago version 11.

RESULTS

Baseline characteristics are presented in Table 1. Mean age was 58 years and 76% of patients were male. The full range of severity of CHF from NYHA I to IV was present with a mean NYHA of 2.3±0.8. All patients received RAS-inhibition (85% ACE-inhibitor) and a large proportion received also β-blockers and diuretics.

Table 1. Baseline characteristics

	Total Population *(n=101)*
Age (years)	58.1 ± 11.7
Sex (n, % male)	77 (76)
NYHA class	2.3 ± 0.8
LVEF	0.28 ± 0.09
Ischemic etiology (n, %)	47 (47)
Medication	
RAS-inhibition (n, % use)	101 (100)
β-blocker (n, % use)	85 (85)
Spironolactone (n, % use)	36 (36)
Diuretics (n, % use)	68 (69)
Physical examination	
Heart rate (bpm)	65 ± 13
Systolic BP (mm Hg)	120 ± 20
Diastolic BP (mm Hg)	69 ± 12
BMI (kg/m^2)	27 ± 4
Serum creatinine (umol/L)	112 ± 34
Renal measurements	
ERPF (mL/min)	324 ± 114
GFR (mL/min)	89 ± 35
Filtration Fraction (%)	27 ± 5

NYHA; New York Heart Association functional class, LVEF; left ventricular ejection fraction, RAS; renine-angiotensin system, BP; blood pressure, BMI; body mas index, ERPF; effective renal plasma flow, GFR; glomerular filtration rate

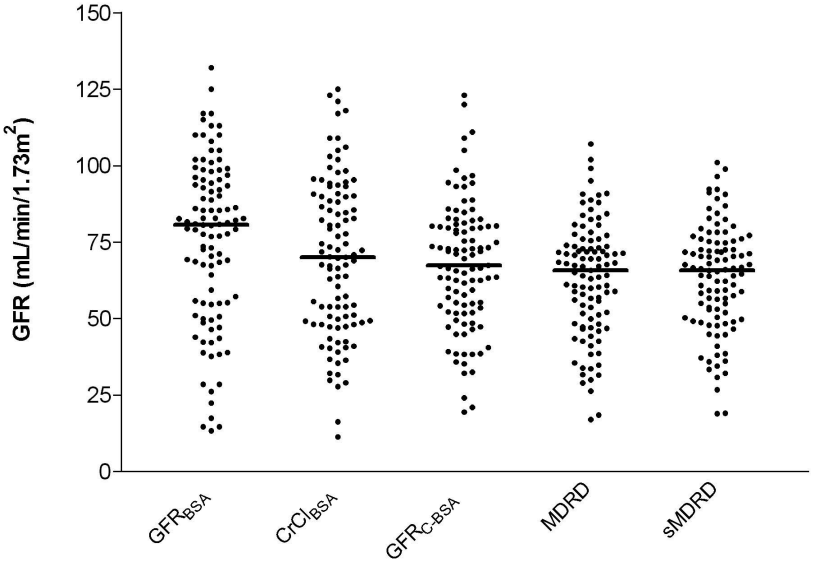

Figure 1A. Scatterplot of the distribution of the true GFR_{BSA}, $CrCl_{BSA}$ and creatinine-based formulas.

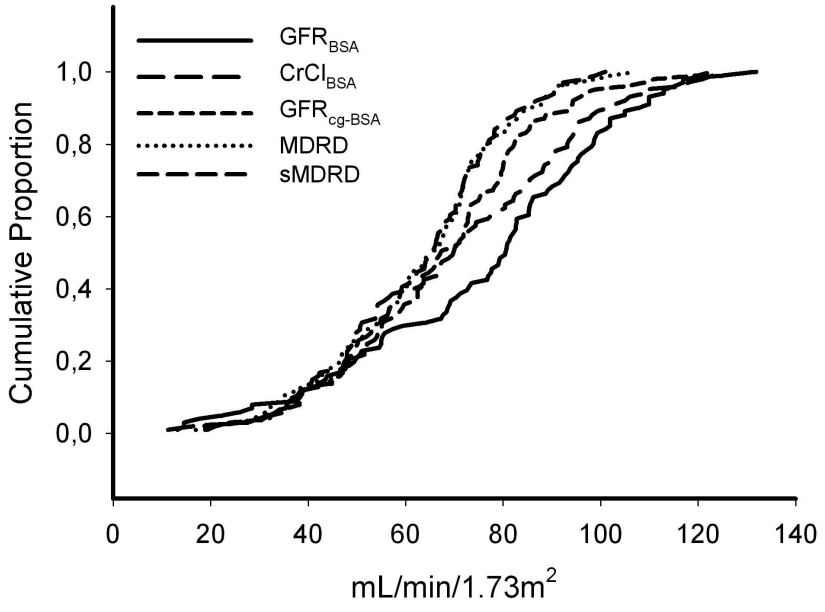

Figure 1B. Cumulative distributions of the true GFR_{BSA}, $CrCl_{BSA}$ and creatinine-based formulas.

The mean true GFR of this population was 89 mL/min, ranging from 12-156 mL/min. Mean CrCl was 83±34 mL/min with a bias of –6% (±2SD; -47%/ 68%; $P < 0.001$) and a precision of r^2=0.64. In 81% of the subjects the CrCl was within the 30% range of the true GFR. GFR_{cg} was 80±29 mL/min, with a bias of –8% (±2SD; -45%/ 55%; $P < 0.001$) and a precision of r^2=0.69. In 76% of the subjects the value of GFR_{cg} was within the 30% range of true GFR. Individual values of the true GFR_{BSA}, the creatinine-based formulas and $CrCl_{BSA}$ are presented in Figure 1A. Cumulative distributions of the true GFR_{BSA}, $CrCl_{BSA}$ and creatinine-based formulas are shown in Figure 1B. This figure shows that as GFR_{BSA} > 55 mL/min/1.73m^2 all creatinine based formulas and $CrCl_{BSA}$ underestimate GFR_{BSA}.

In Table 2 the predictive performances of the creatinine-based formulas and $CrCl_{BSA}$ are presented. All creatinine-based formulas and $CrCl_{BSA}$ significantly underestimated GFR_{BSA} as measured by iothalamate clearance. MDRD had the highest precision (r^2=0.71), but also the highest bias (13%). The validity of the creatinine-based formulas according to Bland-Altman analyses is shown in Table 2 and graphically depicted in Figures 2A-D that show the mean differences between GFR_{BSA} and the creatinine-based formulas with the lines of agreement (mean ± 2SD). The agreement with true GFR_{BSA} was best for the MDRD. Furthermore, these figures illustrate an underestimation in the higher range of renal function, as of a GFR_{BSA} of approximately 65 ml/min/1.73m^2 and an overestimation in the lower range of renal function, below a GFR_{BSA} of approximately 35 ml/min/1.73m^2. Interestingly, all creatinine-based formulas underestimate GFR_{BSA} systematically, but $CrCl_{BSA}$ does not. Also, this systemic deviation is more pronounced in both MDRD formulas compared to $GFR_{cg\text{-}BSA}$.

To analyse for the determinants of the systematic error, we evaluated the predictive performance of the creatinine-based formulas in subgroups by a break-up by variables included into the formulas (Table 3). Especially in the low and high ranges of serum creatinine

Table 2. Predictive performances of creatinine-based formulas and creatinine clearance in CHF.

	Mean	Min/Max	Precision	Accuracy¶		Bias	
			r^2	15%	30%	Mean (%)	±2SD (%)
GFR_{BSA}	75±27	13-133	-			-	-
$CrCl_{BSA}$	70±25†	11-125	0.56	48	81	-6	-47/ 66
$GFR_{cg\text{-}BSA}$	67±21*	19-123	0.62	47	76	-7	-45/ 55
MDRD	63±19*	17-108	0.71	41	83	-13	-45 / 36
sMDRD	63±18*	19-103	0.68	42	79	-12	-46/ 43

*†P < 0.01 with GFR_{BSA}, and * P < 0.001 with GFR_{BSA}.*
¶ Percentage within specified range of GFR_{BSA}.
GFR_{BSA}; glomerular filtration rate BSA corrected, $CrCl_{BSA}$; creatinine clearance BSA corrected, $GFR_{cg\text{-}BSA}$; Cockcroft Gault formula BSA corrected, MDRD; modified diet in renal dysfunction, sMDRD; simplified modified diet in renal dysfunction

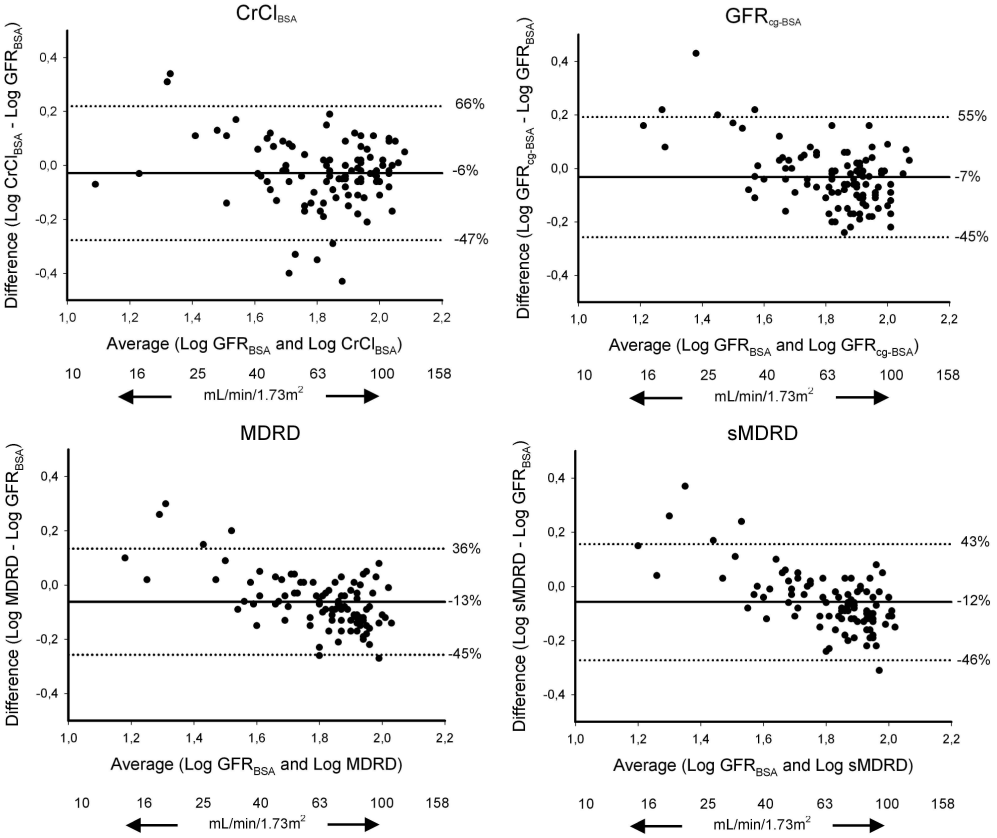

Figure 2A-D. Bland-Altman scatterplots of the distribution of the true GFR_{BSA}, $CrCl_{BSA}$ and creatinine-based formulas.

and urea the creatinine-based formulas are invalid in estimating GFR_{BSA}. In patients with low serum creatinine or urea the bias was larger. Furthermore, weight appeared a moderately important confounder in the MDRD formulas.

In Table 4 the bias is shown for subgroups divided into tertiles for other clinical parameters. Several variables reflect the severity of CHF, such as LVEF and NYHA class, but also blood pressure and ERPF. LVEF was only a weak confounder when compared with NYHA class, ERPF and blood pressure. In patients with a high NYHA class (III+IV) and in patients with low blood pressure (systolic and diastolic) or low ERPF the formulas performed better. In patients with mild CHF bias was increased for all formulas, especially in the higher ranges of ERPF. In patients with severe CHF precision and accuracy were improved (data not shown), and the bias was decreased.

Table 3. Bias of the formulas stratified to variables included into the formulas.

	$GFR_{cg\text{-}BSA}$		MDRD		sMDRD	
	Bias		*Bias*		*Bias*	
	Mean (%)	*95% CI*	*Mean (%)*	*95% CI*	*Mean (%)*	*95% CI*
Age (years)						
<55	2	-49/79	-15	-46/34	-15	-49/42
55-62	-10*	-40/35	-15	-45/31	-14	-45/34
>62	-14*	-49/47	-10	-44/44	-8	-44/53
Gender						
Male	-11	-42/37	-15	-42/27	-14	-43/30
Female	5*	-47/105	-9	-50/65	-7	-53/84
Weight (kg)						
<78	-8	-51/73	-8	-45/54	-6	-47/68
78-93	-8	-42/47	-12	-41/32	-11	-43/38
>93	-6	-40/47	-19*	-46/20	-20*	-46/18
Creatinine (μmol/L)						
<93	-14	-43/30	-17	-41/17	-17	-42/18
93-115	-9	-41/41	-18#	-42/16	-18#	-44/19
>115	3*	-46/99	-6*	-48/71	-3*	-49/85
Urea (mmol/L)						
<6.3	-14	-44/ 30	-19	-43/ 15	-22	-45/ 10
6.3-8.1	-14#	-40/ 24	-17#	-41/ 17	-16#	-41/ 20
>8.1	9*	-40/ 98	-2*	-43/ 68	3*	-42/ 82
Albumin (g/L)						
<40	-11	-41/ 35	-16	-40/ 16	-14	-39/ 23
40-43	-13	-46/ 40	-16	-47/ 33	-16	-49/ 40
>43	2	-43/ 85	-7	-43/ 53	-8	-47/ 62

**P<0.05 compared to the first tertile.*
 # P<0.05 compared to the third tertile.
$GFR_{cg\text{-}BSA}$; Cockcroft Gault formula BSA corrected, MDRD; modified diet in renal dysfunction, sMDRD; simplified modified diet in renal dysfunction

Table 4. Bias of the formulas stratified to clinical parameters.

	$GFR_{cg\text{-}BSA}$		MDRD		sMDRD	
	Bias		*Bias*		*Bias*	
	Mean (%)	*95% CI*	*Mean (%)*	*95% CI*	*Mean (%)*	*95% CI*
NYHA (class)						
I+II	-16	-42/21	-20	-43/13	-20	-43/14
III+IV	8*	-38/90	-2*	-41/61	0*	-42/74
LVEF						
<0.23	-1	-33/47	-9	-34/26	-9	-36/28
0.23-0.33	-6	-49/74	-11	-49/56	-9#	-49/65
>0.33	-14*	-47/38	-19*	-46/21	-19*	-49/30

Etiology						
Ischemic	-10	-44/ 43	-14	-47/37	-14	-48/43
Non-ischemic	-5	-45/ 66	-12	-43/36	-11	-44/44
Heart rate (bpm)						
<58	-11	-43/ 44	-14	-42/27	-13	-42/13
58-70	0	-41/61	-10	-41/69	-8	-44/50
>70	-10	-49/ 57	-14	-49/44	-15	-52/51
Syst. BP (mm Hg)						
<110	7	-36/ 78	-7	-41/46	-5	-44/61
110-125	-13*	-43/ 31	-18*	-43/18	-18*	-44/20
>125	-14*	-48/ 42	-15	-48/30	-14	-48/43
Diast. BP (mm Hg)						
<62	1	-42/74	-8	-42/44	-5	-42/57
62-75	-9	-44/47	-13	-46/39	-14	-47/40
>75	-13*	-47/42	-18*	-46/24	-18*	-48/30
BMI (kg/m^2)						
<26	-8	-51/75	-5	-46/66	-4	-49/81
26-29	-8	-40/42	-14	-40/23	-13	-40/26
>29	-6	-42/51	-20*	-44/14	-19*	-44/17
Creatinine production						
<1.11	2	-44/85	-2	-40/61	0	-43/76
1.11-1.58	-8	-43/47	-13*	-42/31	-12*#	-43/35
>1.58	-14*	-42/27	-22*	-44/10	-22*	-44/7
ERPF (mL/min/1.73m^2)						
<239	3	-41/79	-3	-48/54	1	-38/66
239-328	-13*	-41/29	-18*	-42/15	-18*	-41/14
>328	-17*	-45/26	-24*	-48/12	-25*	-49/11
FF (%)						
<26	6	-41/92	-2	-44/69	0	-46/84
26-29	-13*	-43/32	-15*	-38/18	-15*	-39/18
>29	-13	-43/33	-21	-44/11	-20	-45/17
Medication						
β-blocker						
No	-6	-52/81	-10	-47/51	-8	-50/69
Yes	-8	-44/51	-14	-45/34	-13	-46/39
Diuretic						
No	-19	-42/16	-20	-42/10	-20	-41/9
Yes	-2*	-43/69	-10*	-45/47	-9*	-47/57
Spironolactone						
No	-15	-43/27	-18	-44/20	-18	-45/22
Yes	8*	-38/88	-4*	-42/58	-1*	-43/72

**P<0.05 compared to the first tertile.*
 # P<0.05 compared to the third tertile.
NYHA; New York Heart Association functional class, LVEF; left ventricular ejection fraction, BP; blood pressure, BMI; body mas index, ERPF; effective renal plasma flow, FF; filtration fraction, $GFR_{cg\text{-}BSA}$; Cockcroft Gault formula BSA corrected, MDRD; modified diet in renal dysfunction, sMDRD; simplified modified diet in renal dysfunction.

DISCUSSION

This is the first study that validated different, creatinine-based formulas and $CrCl_{BSA}$, with true renal function measurements in CHF patients. The formulas were significantly biased; because they overestimated GFR at low values and underestimated GFR at near-normal values. The most accurate renal function estimates were derived in patients with severe CHF.

Recent analyses of the influence of renal function on clinical outcome in patients with CHF have confirmed its relevance in cardiovascular prognosis. An accurate measurement of renal function is therefore an essential tool in individual risk assessment. The methods used in this study to estimate GFR are the most common and widely used. We observed that $CrCl_{BSA}$ had a low bias, but the variance was wide, making this a poor alternative for estimating renal function on an individual level. CrCl is often seen as an accurate tool to measure renal function, but the K/DOQI guidelines state that CrCl is not more accurate than creatinine-based formulas[16], because the reliability of CrCl is dependent on patient compliance of collecting 24h urine accurately. Moreover in subjects with moderate to severe renal function impairment its accuracy is impaired by active creatinine secretion by the tubulus.[6]

The MDRD formula is the formula with the highest precision, but also the formula with the largest estimated biased over a range of GFR_{BSA} levels with comparable accuracy compared to the other formulas. This means that the MDRD has a more systematic deviation (bias) from the true GFR_{BSA}, which is readily apparent from the Bland-Altman figures. The systematic deviation of the MDRD is an important finding, because a systematic deviation can in principle be corrected by a correction factor, whereas lack of precision cannot be corrected in this manner, but will need additional covariates subject to measurement error.[14] Most studies do not use the MDRD, which requires data on both serum urea and serum albumin, but the sMDRD instead. In our patients with CHF this formula had a similar predictive performance as the MDRD, whereas in $GFR_{cg\text{-}BSA}$ the systemic deviation was less pronounced.

Creatinine-based formulas have been validated in a variety of patient populations, mostly community-based or with chronic renal disease.[14;17] Using a formula in a different population without adequate validation, such as CHF, requires great caution, as is shown by our study. One might expect in this population that these formulas would potentially overestimate the GFR_{BSA} by changes in body composition. First, malnutrition, inactivity and cachexia are common in CHF. The resulting reduced muscle mass leads to reduced creatinine production[13;18], which leads to overestimation of GFR_{BSA}.[13] Second, increased extracellular volume in CHF patients, due to sodium retention, reduces muscle mass relative to healthy subjects of the same body weight, again leading to less creatinine production per unit of body weight. Third, some tubular secretion of creatinine can occur, that leads to overestimation of the true GFR_{BSA}. However, this problem might only be present in the Cockcroft-Gault formula, because this formula is intended to estimate the CrCl, whereas both MDRD formulas are intended to estimate the true GFR_{BSA}.

In contrast to these expectations we found overestimation of true GFR_{BSA} by all formulas in the lower ranges of renal function, i.e below 35 mL/min/1.73m^2. In populations with primary renal disease this has mainly been reported in pre-dialysis ranges of GFR_{BSA}[19], therefore, the current overestimation in less severe renal dysfunction might be typical for CHF. The primarily hemodynamic nature of the renal function impairment in CHF might be relevant here. CHF is characterised by low blood pressure and reduced renal perfusion pressure[20] leading to reduced filtration rate in otherwise viable nephrons with intact tubuli. This may lead to a relatively large impact of tubular secretion of creatinine, as compared to primary renal diseases where generally loss of glomeruli leads to loss of the corresponding tubuli as well.

In the near-normal values of renal function all formulas underestimated the true GFR_{BSA}. As shown in Table 2 all formulas had a larger bias in the lower values of serum creatinine, which is in line with several other studies.[14;21] There are several possible explanations. First, during the development of a creatinine based formula correction factors derived from the sample data were used. It should be recognised that the use of such a correction factor introduces a bias, because those factors were derived from renal diseased populations and are dependent on the level of GFR, since tubular secretion of creatinine increases with decreasing GFR. Second, serum creatinine does not rise in the early stages of impaired renal function, due to compensatory mechanisms.[22] Therefore formulas cannot differentiate between normal and mildly affected renal function[13], and underestimate in normal or mildly affected range of GFR_{BSA}. Another explanation is suggested by Rule et al[17], who states that the variability of serum creatinine levels in healthy subjects is largely dependent on muscle mass and dietary protein intake, and therefore serum creatinine has a weak coefficient in predicting GFR. In patients with renal disease on the other hand, the variability in serum creatinine levels is largely dependent on GFR and therefore serum creatinine has a strong coefficient in predicting GFR.[17]

Besides serum creatinine other parameters included into the formulas, like gender, influenced the predictive performance. However, in our population females had worse renal function (80 mL/min/1.73m^2 vs. 61 mL/min/1.73m^2), and the formulas appeared to perform better in the lower ranges of renal function. Another potential confounder might be age. We showed that the impact of age was only moderate, probably due to the fact that the formulas perform better in higher serum creatinine levels and serum creatinine increases with age. Especially the MDRD formulas showed improved predictive performances in elderly people with CHF.

The performance of the formulas varies within the subgroups of our CHF population (Table 4). For this reason it could be argued that the selected formula should be tailored on the study population of interest. For example, in an obese population the MDRD formulas would not be a good option and preferably the Cockcroft-Gault should be used. Concomitant medication interacting with renal function like spironolactone and diuretics seemed to influence the predictive performance. However, there is possible a prescription bias. These medications are more often prescribed to patients with worse symptomatic CHF, and these patients also have worse renal function.

Implications

The value and usefulness of renal function formulae in clinical practice is dependent on the precision and bias of the calculated value. The degree of variation that is acceptable will depend on the particular clinical situation in which the formula is used. The main implications of this study for daily practice are clear; creatinine-based formulas and $CrCl_{BSA}$ are not a good option to measure GFR_{BSA} in the individual patient with CHF. First, the variance is too wide, ±30 mL/min/1.73m^2, second, the overestimation of GFR_{BSA} in the lower ranges can endanger the patient if one is not aware of this systematic deviation. This is particularly important in elderly patients in whom age-related physiological changes result in reduced renal function and e.g. changes in drug pharmacokinetics and pharmacodynamics. Furthermore, these formulas are not reliable in a situation of long-term monitoring of renal function in CHF. CHF is a progressive condition and this study shows that the predictive performance of these formulas changes across the spectrum from mild to severe CHF; from underestimation to overestimation. This means that, although estimated renal function can appear to be stable during worsening of CHF, it may in fact be declining.

Limitations

In this study all patients were using renin-angiotensin-system inhibitors (Angiotensin II Converting Enzyme-Inhibitors or Angiotensin II receptor-Type 2-antagonists). These medications could have influenced the true GFR. In addition, the formulas were developed, especially the Cockcroft-Gault formula, in populations with less use of renin-angiotensin-system inhibitors. This could have influenced the differences observed between the GFR and the formulas.

CONCLUSION

All formulas underestimated GFR_{BSA} in the near-normal and normal range of renal function, and overestimated GFR_{BSA} in the low and very low values, although the predictive performance improved in patients with severe CHF. The MDRD formula is the most precise but also the most biased formula over a range of GFR_{BSA}, which makes this formula, after adequate adjustment, the most useful in clinical practice.

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