Symmetrical Dimethylarginine Outperforms CKD-EPI and MDRD-Derived eGFR for the Assessment of Renal Function in Patients with Adult Congenital Heart Disease

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Key Words

Adult congenital heart disease • Glomerular filtration rate • Glomerular filtration rate formula

Abstract

Background/Aims: Adults with congenital heart disease exhibit a 3-fold higher mortality in the presence of chronic kidney disease, hence assessment of renal function is crucial in this patient population. Formulas for the estimation of glomerular filtration rate (GFR) have not been evaluated in this patient population. Therefore, this study compares different markers and equations for the estimation of renal function in adults with congenital heart disease. **Methods:** Renal function was assessed in 102 patients using the Modification of Diet in Renal Disease (MDRD) equation, the simplified MDRD equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the Cockcroft-Gault formula. Additionally, symmetrical dimethylarginine (SDMA) was measured. Those parameters were compared to cystatin C-derived GFR using the Larsson equation. **Results:** GFR estimates using the original MDRD ($r = 0.465$, $p < 0.001$) and the CKD-EPI equation ($r = 0.462$, $p < 0.001$) showed a similar strong correlation with the cystatin C-based eGFR equation, while eGFR using the simplified MDRD equation showed a

slightly weaker correlation ($r = 0.439$, $p < 0.001$). The Cockcroft-Gault formula showed no correlation at all to the cystatin C-based eGFR ($r = 0.144$, $p = 0.17$). The strongest correlation was observed for SDMA and cystatin C-based eGFR ($r = -0.552$, $p < 0.001$). **Conclusion:** GFR in adults with congenital heart disease should be estimated using the original MDRD or the CKD-EPI formula. SDMA seems to be a promising marker of renal function for this patient group.

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Introduction

Formulas for the estimation of glomerular filtration rate (GFR) have rarely been evaluated in special patient populations. Adults with congenital heart disease exhibit a 3-fold higher mortality with a moderate or severe reduction in GFR [1]. However, GFR cannot be measured by direct means but by determination of urinary clearance of filtration markers. The gold standard, inulin clearance, is cumbersome and expensive, reducing its utility in clinical practice, which holds also true for esti-

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mations using the clearance of radioisotopes [2]. Dimopoulos et al. [1] calculated GFR in adult patients with congenital heart disease using the Modification of Diet in Renal Disease equation (MDRD). This equation has some limitations. Its accuracy is reduced in the state of normal or slightly diminished renal function. To overcome this problem the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was recently introduced [3]. This equation is more accurate than the MDRD study equation, especially in subjects with normal or slightly impaired renal function. Also, the CKD-EPI formula has been evaluated across various study populations and clinical conditions [3].

The accuracy of these formulas in patients with cardiovascular disease has not been well substantiated [4]. Therefore, a search for new markers and equations for the assessment of renal function has begun. Lately, two markers which show promise are serum cystatin C and symmetrical dimethylarginine (SDMA). Serum cystatin C concentration is a better marker of renal dysfunction (that is, reduced GFR) than plasma creatinine concentration, at least in elderly subjects with plasma creatinine concentrations within the normal range. Also SDMA, the structural isomer of the endogenous nitric oxide inhibitor asymmetric dimethylarginine, has been found to be a reliable marker of renal function [5]. This 202-Da compound was first detected in human urine [6] and seems to be exclusively eliminated by renal excretion [7]. A meta-analysis of 18 studies involving a total of 2,136 patients showed a strong correlation between SDMA and different parameters of renal function [5].

The aim of this study was to compare different markers and equations for the estimation of renal function to cystatin C-based GFR in adults with congenital heart disease.

Methods

The patients were recruited during an outpatient visit at our Adult Congenital Heart Disease Clinic. All patients in whom a venous blood sampling was feasible were eligible for this study. The study was approved by the Ethics Committee of Hannover Medical School, Hannover, Germany. All patients gave written informed consent.

The severity of the congenital heart defect was graded according to recent recommendations [8].

Laboratory Methods

Blood samples for measurement of plasma SDMA, cystatin C and routine chemistry were drawn. Blood samples were immediately cooled on ice, centrifuged at 1,500 g and 4°C for 10 min. Supernatants were stored in 1-ml aliquots at -80°C until further use.

Plasma concentrations of SDMA were measured applying a recently developed liquid-chromatography mass-spectrometry method described elsewhere [9]. All other measurements were done with routine laboratory tests using certified assay methods.

Estimation of Kidney Function

GFR according to the Cockcroft-Gault formula [10]: Creatinine clearance = $(140 - \text{age}) \times (\text{weight in kg}) / 72 \times \text{Scr} \times 0.85$ (if female), where Scr is serum creatinine (mg/dl).

GFR according to the MDRD equation [11]: $\text{GFR} = 170 \times [\text{Scr}]^{-0.999} \times [12]^{-0.176} \times 0.762$ (if female) $\times 1.180$ (if black) $\times [\text{SUN}]^{-0.170} \times [\text{Alb}]^{+0.318}$, where Scr is serum creatinine concentration (mg/dl), Alb is serum albumin concentration (g/dl) and SUN is serum urea nitrogen concentration (mg/dl).

GFR according to the simplified MDRD equation [12]: $\text{GFR} = 186 \times \text{Scr}^{-1.154} \times \text{age}^{-0.203} \times 1.212$ (if black) $\times 0.742$ (if female), where Scr is serum creatinine (mg/dl).

GFR according to the CKD-EPI equation [3]: $\text{GFR} = 141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ (if female) $\times 1.159$ (if black), where Scr is serum creatinine (mg/dl), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1.

GFR according to the Larsson equation [13]: $\text{GFR} = 77.24 \times \text{Scyc}^{-1.2623}$, where Scyc is serum cystatin C.

Statistical Analysis

We used SPSS 15.0 for statistical analysis. Continuous data are presented as means $\pm$ standard deviation. Categorical data are presented as counts and proportions. Patient demographic and clinical characteristics were summarized as means $\pm$ standard deviation. For correlation Pearson's correlation coefficient was calculated. The significance level was set at $p < 0.05$.

Results

One hundred and two patients were enrolled in our cross-sectional study. Due to incomplete data sets 5 patients were excluded and the final analysis is based on 97 patients. Table 1 shows the clinical characteristics of the study population. Overall renal function of patients with congenital heart disease was not impaired. The number of patients in the different GFR stages was as follows: 60–90 ml/min/1.73 m², 4 patients; >90 ml/min/1.73 m², 93 patients.

GFR estimated by the original MDRD (Pearson $r = 0.465$, $p < 0.001$) and the CKD-EPI equation ($r = 0.462$, $p < 0.001$) showed a similar strong correlation with the eGFR based on a cystatin C-based equation (fig. 1). While GFR according to the simplified MDRD equation showed a slightly weaker correlation ($r = 0.439$, $p < 0.001$), creatinine clearance according to the Cockcroft-Gault formula showed no correlation at all to the cystatin C-based

eGFR ($r = 0.144$, $p = 0.17$). The strongest correlation was observed for SDMA and cystatin C-based eGFR ($r = -0.552$, $p < 0.001$) (fig. 1).

Discussion

In this study, GFR estimated by the CKD-EPI equation performed equally well as GFR estimated by the original MDRD equation. Both formula-based estimates of GFR were outperformed by SDMA.

The CKD-EPI equation has several advantages compared to the MDRD study equation. The later was developed by studying people with chronic kidney disease, and as such, its major limitations are imprecision and systematic underestimation of measured GFR at higher values [3]. The CKD-EPI equation has lower bias, especially at an estimated GFR greater than 60 ml/min per 1.73 m² [3]. Further, one additional parameter needed for the MDRD study equation is albumin, while for the CKD-EPI formula only creatinine has to be measured. Therefore, the CKD-EPI equation is more cost-effective. The simplified MDRD equation used by Dimopoulos et al. [1] showed a slightly weaker correlation with the cystatin C-based GFR than the CKD-EPI equation in our study. Therefore, if a creatinine-based formula for GFR estimation is used in adults with congenital heart disease it should be the CKD-EPI equation. The Cockcroft-Gault formula-derived creatinine clearance showed no correlation with the cystatin C-based GFR, suggesting its limited practical applicability to this patient group.

SDMA showed the tightest correlation to a cystatin C-based eGFR estimation. SDMA is the structural isomer of asymmetric dimethylarginine. A recent meta-analysis showed that plasma SDMA levels correlate with several parameters of renal function [5]. Moreover, SDMA increases rapidly after acute reduction in GFR [14]. Although there is an excellent correlation between SDMA and established estimates of GFR, it is not known if SDMA fulfils all criteria for an ideal GFR marker, that is stable production rate not affected by other diseases, free glomerular filtration and lack of tubular reabsorption [5]. Further, we lack sensitivity and specificity data for SDMA in humans. Also, the high cost of the laboratory methods to measure SDMA is still prohibitive for widespread clinical application. We therefore suggest that CKD-EPI-based eGFR should be used in adults with congenital heart disease in everyday clinical practice.

We wish to point out limitations of our study. Firstly, we did not use the gold standard for GFR measurement,

Table 1. Clinical characteristics of study population

Age, years	30.2 ± 10.4
Sex, % female	41.2
BMI	23.6 ± 4.3
Complexity of congenital heart disease, %	
Simple	19.6
Moderate	37.1
Severe	43.3
Creatinine, µmol/l	69.6 ± 12.0
Cystatin C, mg/l	0.69 ± 0.15
SDMA, µmol/l	0.53 ± 0.13
GFR, ml/min	
Cockcroft-Gault	130.9 ± 33.5
MDRD	111.0 ± 21.1
Simplified MDRD	114.0 ± 21.7
CKD-EPI	113.9 ± 14.8
Larsson	129.2 ± 26.3
GFR, ml/min with Larsson formula	
NYHA I (n = 56)	132.1 ± 19.8
NYHA II (n = 21)	130.3 ± 27.7
NYHA III (n = 17)	124.5 ± 38.4
NYHA IV (n = 3)	95.1 ± 26.0

Results are means ± standard deviation unless otherwise stated.

that is, inulin clearance or iohexol clearance, but instead relied on cystatin C as our gold standard. However, a study in cardiac patients showed a strong correlation of cystatin C to iopromide clearance [15]. The reliability of cystatin C is also supported by the results of a recent meta-analysis in which it was clearly superior to creatinine as a marker of GFR [16]. In a study of 140 patients with various renal diseases, the reciprocal serum cystatin C level was positively correlated with inulin clearance ($r = 0.882$) [17]. A recent meta-analysis of the diagnostic accuracy of cystatin C for the estimation of renal dysfunction compared to inulin clearance reported that the ability of cystatin C to rule in renal impairment (as measured by inulin-determined GFR of 60–79 ml/min/1.73 m²) in persons in whom this is suspected is large and conclusive [18]. Further, Jonsson et al. [19] reported that estimated GFR from serum cystatin C shows strong agreement with iohexol clearance in patients with low GFR. Therefore, it is reasonable to use a cystatin C-based GFR estimation as a gold standard if inulin or iohexol clearance is not available. The second limitation of our study is the low prevalence of patients with severe renal impairment, reducing the variety, hence the spread of the different markers. Yet our patient population is the second largest in adult patients with congenital heart disease

Fig. 1. Correlation of Cystatin C-based GFR with different markers and GFR equations. The strongest correlation is observed for SDMA ($r = -0.552$) (a). GFR estimated by the CKD-EPI ($r = 0.462$) (b) and the original MDRD equation ($r = 0.465$) (c) show a similar strong correlation. GFR according to the simplified MDRD equation shows a slightly weaker correlation ($r = 0.439$) (d) and creatinine clearance according to the Cockcroft-Gault formula shows no correlation at all ($r = 0.144$) (e).

in which different parameters of renal function have been measured.

We conclude that currently in adults with congenital heart disease GFR should be estimated using the CKD-EPI formula. SDMA might be a promising marker of renal function (in this patient population) that should be further evaluated.

Disclosure Statement

The authors declare no conflict of interest.

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