Validity of Estimated Glomerular Filtration Rates for Assessment of Baseline and Serial Renal Function in Patients With Atherosclerotic Renal Artery Stenosis Implications for Clinical Trials of Renal Revascularization

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Background—Despite routine use of estimated glomerular filtration rates (GFRs) as major renal end points in clinical trials of renal revascularization, serial GFR estimates have never been validated in patients with renal artery stenosis (RAS). The purpose of this study was to evaluate the validity of GFR estimates in patients with atherosclerotic RAS.

Methods and Results—Serum creatinine (SCr) and $^{125}$I-iothalamate GFR (I-GFR) were measured in patients with RAS. GFR estimates were calculated from Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Cockcroft-Gault (CG) formulas. Using I-GFR as the reference standard, the sensitivity, specificity, and receiver operating characteristic area under the curve (AUC) were determined for MDRD, CKD-EPI, CG, and reciprocal SCr for identifying I-GFR $\leq 60$ mL/min per 1.73 m$^2$ and a 20% change in I-GFR over time. Between 1998 and 2007, 541 I-GFR measurements were performed in 254 consecutive patients with RAS. MDRD, CKD-EPI, and CG GFR estimates demonstrated good sensitivity (86% to 95%), modest specificity (67% to 71%), and good reliability (AUC, 0.86 to 0.94) for identifying I-GFR $< 60$ mL/min per 1.73 m$^2$. GFR estimates had good specificity (87% to 95%), poor sensitivity (0% to 45%), and poor reliability (AUC, 0.61 to 0.65) for detecting 20% changes in I-GFR over follow-up.

Conclusions—In patients with RAS, GFR estimates demonstrate good sensitivity and modest specificity for identifying I-GFR $\leq 60$ mL/min per 1.73 m$^2$ but poor sensitivity and reliability for detecting 20% changes in I-GFR. GFR estimates should not be used in clinical trials as major end points to assess serial GFR after renal revascularization. (Circ Cardiovasc Interv. 2011;4:219-225.)

Key Words: renal artery obstruction • stents • glomerular filtration rate

Atherosclerotic renal artery stenosis (RAS) is a common finding among patients with chronic kidney disease (CKD) and may lead to renal dysfunction. Renal function is commonly assessed with glomerular filtration rate (GFR) estimates based on serum creatinine (SCr). GFR estimates originally were developed to assess baseline renal function and identify patients with CKD. Although GFR estimates have been used to evaluate serial changes in renal function after revascularization, GFR estimates have not been validated for this purpose. However, filtration function can be directly measured using $^{125}$I-iothalamate GFR (I-GFR), which is the standard against which GFR estimates originally were validated in patients with CKD. Whereas several observational studies report improvement in GFR estimates in patients with RAS after revascularization, randomized trials comparing medical therapy and renal stenting have failed to demonstrate any renal benefit, relying on 20% changes in GFR estimates as major primary and secondary end points. Accordingly, the purpose of this study was to evaluate the validity of GFR estimates for assessing baseline and serial changes in renal function in patients with RAS using directly measured I-GFR as the reference standard.

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Methods

Patient Selection
Between 1998 and 2007, we routinely measured SCr and I-GFR in patients with RAS, which was defined as a diameter stenosis $\geq 50\%$ in $\geq 1$ renal artery by CT angiography, magnetic resonance angiography, or invasive imaging. For this study, patients with RAS were included if SCr was measured by the Beaumont Reference Laboratory (Royal Oak, MI) using the modified Jaffé
reaction indirectly traceable to isotope dilution mass spectrometry (Roche Modular Instruments, Roche Diagnostics) within 14 days of I-GFR, patients were taking stable doses of antihypertensive and diuretic medications between SCr and I-GFR measurements, and exposure to iotidated radiographic contrast did not occur within 1 month before I-GFR or SCr measurement. For patients undergoing serial assessment of I-GFR during the study period, I-GFR values were excluded if the nearest SCr was measured >14 days from I-GFR. Baseline clinical variables on all patients were ascertained by structured chart abstraction. This study was approved by the Human Investigations Committee of William Beaumont Hospital.

I-GFR Technique
I-GFR was measured as the plasma disappearance of $^{125}\text{I}$-iothalamate using a 2-compartment pharmacokinetic model. Blood samples were drawn 5, 10, and 15 minutes after administration of 0.15 mL of $^{125}$I-iothalamate (25 to 40 μCi) and at 30-minute intervals starting at least 3 hours after administration. All samples were timed to the nearest 0.1 minute after $^{125}$I-iothalamate administration.

Estimated GFR
GFR estimates were calculated according to the 4-variable Modification of Diet in Renal Disease (MDRD), CKD Epidemiology Collaboration (CKD-EPI), and Cockcroft-Gault (CG) formulas, as follows: 

\[
\text{MDRD GFR} = \frac{186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212 \text{ (if black)}}{0.742 \text{ (if female)}} \\
\text{CKD-EPI GFR} = \frac{141 \times \min(\text{SCr/κ, 1})^{0.9937} \times 1.018 \text{ (if female)}}{1.159 \text{ (if black)}} \\
\text{CG GFR} = \frac{[140 - \text{age}] \times \text{weight} / (72 \times \text{SCr}) \times 0.85 \text{ (if female)}}
\]

For the CKD-EPI GFR calculation, $\kappa$ is 0.7 for female sex and 0.9 for male sex. $\alpha$ is $-0.329$ for female sex and $-0.411$ for male sex, $\min$ indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1. CG GFR was calculated from SCr when a measured body weight was available within 30 days of SCr measurement. Because reciprocal SCr (1/SCr) has been used to estimate GFR also, we determined the points of optimal and diuretic medications between SCr and I-GFR measurements, the percent change between consecutive values was determined. Similarly, percent change was calculated for the corresponding serial MDRD, CKD-EPI, and CG GFR estimates and for 1/SCr. Serial changes in GFR also were evaluated by the frequency of doubling of SCr.

Statistical Methods
Pearson correlation coefficients were used to study the correlation between measured I-GFR and GFR estimates, and the correlation between percent changes in serial I-GFR and GFR estimates. An unweighted $\kappa$ statistic was generated to assess the degree of agreement between 20% changes in I-GFR and 20% changes in serial GFR estimates. The bias and precision of GFR estimates were assessed by Bland-Altman analysis using the median difference and interquartile range for differences between GFR estimates and I-GFR. To assess the accuracy of GFR estimates in patients with RAS, we calculated the frequency of GFR estimates within 30% of I-GFR and the frequency correctly classifying CKD stage. The $\chi^2$ test was used to compare the proportion of GFR estimates and I-GFR <60 mL/min per 1.73 m$^2$. The sensitivity, specificity, positive and negative predictive values, and accuracy of GFR estimates were determined for identifying I-GFR <60 mL/min per 1.73 m$^2$, a 20% increase in I-GFR, and a 20% decrease in I-GFR. We chose to evaluate 20% change in GFR because this threshold has been used as a renal end point in randomized trials of renal revascularization. Receiver operating characteristic curves were constructed, and the area under the curve (AUC) was calculated for each GFR estimate identifying I-GFR <60 mL/min per 1.73 m$^2$ and a 20% increase or decrease in I-GFR. AUC measures the reliability of the estimates to identify measured GFR and was characterized as follows: excellent (AUC $\geq$0.9), good (AUC, 0.8 to <0.9), fair (AUC, 0.7 to <0.8), and poor (AUC<0.7). Using the receiver operating characteristic analysis for identifying I-GFR <60 mL/min per 1.73 m$^2$, we determined the points of optimal sensitivity and specificity for GFR estimates.

Categorical variables are reported as frequencies. Continuous variables, including SCr, age, and time, are reported as mean±SD, and all other variables are reported as median (25th–75th percentile). Bland-Altman analysis was conducted using Microsoft Excel Analysis-IT 2010 (Analyze-it Software, Ltd; Leeds, UK); other analyses were performed using SAS version 9.1.3 (SAS Inc; Cary, NC).

Results
Study Population
Baseline characteristics of the study population are shown in Table 1. Between 1998 and 2007, 771 I-GFR measurements were obtained in 293 consecutive patients with RAS, but 230 I-GFR values were excluded because SCr was not available within 14 days, leaving a total of 541 I-GFR measurements in 254 patients. I-GFR and SCr measurements were performed on the same day in 409 (75.6%) instances, within 3 days in 483 (89.3%), within 1 week in 505 (93.3%), and in the second week in 36 (6.7%).
Body weights were measured within 1 month of SCr measurement in 183 (33.8%) patients.

Comparison of GFR Estimates and I-GFR
During the study period, the measured I-GFR was 53.2±24.2 mL/min per 1.73 m². Corresponding GFR estimates were 48.6±30.5, 46.8±19.9, and 51.5±22.9 mL/min per 1.73 m² using MDRD, CKD-EPI, and CG, respectively. The correlation between I-GFR and GFR estimates was reasonable: MDRD, $r^2=0.83$; CKD-EPI, $r^2=0.85$; CG, $r^2=0.70$; and 1/SCr, $r^2=0.76$ ($P<0.001$ for all) (Figure 1A). The median difference (bias) between the estimates and I-GFR was 3.7±13.5, 5.8±12.6, and 1.0±17.1 mL/min per 1.73 m² using MDRD, CKD-EPI, and CG, respectively. The precision of GFR estimates was characterized by an interquartile range of −3.2 to 12.4, −0.8 to 14.0, and −6.5 to 9.0 mL/min per 1.73 m² for MDRD, CKD-EPI, and CG, respectively. According to the Bland-Altman plots, GFR estimates tended to lose precision (values outside the 95% CI) when I-GFR was >40 mL/min per 1.73 m² (Figure 2A).

Performance of GFR Estimates in the Identification of CKD
I-GFR was <60 mL/min per 1.73 m² in 328 (60.6%) measurements, which is consistent with the diagnosis of CKD, but estimated GFR was <60 mL/min per 1.73 m² in 67.7%, 70.2%,

Figure 1. Correlation of GFR estimates with measured I-GFR. A, Single I-GFR and GFR estimates. B, Percent change in serial I-GFR and GFR estimates. 1/SCr indicates reciprocal serum creatinine; CG, Cockroft-Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; I-GFR, ¹²⁵I-iothalamate glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.
and 66.1% by MDRD, CKD-EPI, and CG, respectively ($P<0.001$ for all compared to I-GFR). Overall, GFR estimates were characterized by good sensitivity (86% to 93%), modest specificity (67% to 71%), and good reliability (AUC, 0.86 to 0.94) for identifying I-GFR < 60 mL/min per 1.73 m$^2$ (Table 2). However, I-GFR was > 60 mL/min per 1.73 m$^2$ in > 25% of cases in which MDRD, CKD-EPI, and CG GFR suggested CKD. The points where sensitivity and specificity were optimized for identifying I-GFR < 60 mL/min per 1.73 m$^2$ were 53.3, 52.6, and 55.1 mL/min per 1.73 m$^2$ for MDRD, CKD-EPI, and CG GFR estimates, respectively. GFR estimates were within 30% of I-GFR in 81.7%, 78.7%, and 75.4% with MDRD, CKD-EPI, and CG respectively, but CKD stage was incorrectly classified by 24.6% to 33.3% of estimates.

Validity of GFR Estimates in the Serial Assessment of Renal Function

There were 287 serial I-GFR measurements obtained 310 ± 223 days after initial measurement. I-GFR changed ≥ 20% in 97 (33.8%) instances, including a 20% increase in 43 (15.0%) and a 20% decrease in 54 (18.8%). Correlations between percent changes in I-GFR and GFR estimates were poor: MDRD, $r^2 = 0.31$ ($P<0.001$); CKD-EPI, $r^2 = 0.32$ ($P<0.001$); CG, $r^2 = 0.27$ ($P=0.07$); and 1/Scr,
Table 2. Diagnostic Performance of Commonly Used GFR Estimates

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>Accuracy, %</th>
<th>AUC</th>
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<td>85.0</td>
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<td>93.0</td>
<td>29.2</td>
<td>86.3</td>
<td>81.5</td>
<td>0.62</td>
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</table>

1/SCr indicates reciprocal serum creatinine; AUC, receiver operating characteristic area under the curve; CG, Cockroft-Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; I-GFR, 125I-iothalamate glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NPV, negative predictive value; PPV, positive predictive value; RAS, renal artery stenosis; SCr, serum creatinine.

$\chi^2=0.31$ (P<0.001) (Figures 1B and 2B). The direction of change in estimated GFR was discordant with the direction of change in I-GFR in 28.0%, 28.0%, and 40.0% of MDRD, CKD-EPI, and CG, respectively. The degree of agreement between serial changes in I-GFR and GFR estimates was poor: MDRD, $\kappa=0.07$ (95% CI, 0.00 to 0.13); CKD-EPI, $\kappa=0.22$ (95% CI, 0.13 to 0.31); CG, $\kappa=-0.06$ (95% CI, -0.13 to 0.01); and 1/SCr, $\kappa=0.04$ (95% CI, -0.03 to 0.10). Doubling of SCr was rare during the study period and occurred in only 3 (1.2%) patients. In fact, 27 (22.5%) patients who experienced a decrease in I-GFR >30% and 8 (6.7%) patients who had a decrease in I-GFR >50% did not double their SCr during the study period. Overall, GFR estimates were characterized by poor sensitivity, good specificity, and poor reliability for identifying a 20% increase (AUC, 0.62 to 0.63) or decrease (AUC, 0.61 to 0.65) in I-GFR (Table 2).

Discussion

Randomized clinical trials comparing medical therapy and renal stenting have relied on GFR estimates as important primary and secondary renal end points and failed to demonstrate any renal benefit of revascularization.3,13–16 The present study shows that GFR estimates are satisfactory screening tests for CKD but lose precision when I-GFR is >40 mL/min per 1.73 m² and are unreliable for detecting a 20% change in I-GFR or for identifying the correct direction of GFR change. Furthermore, correlations between percent changes in I-GFR and GFR estimates as well as the degree of agreement between serial changes in I-GFR and GFR estimates are poor. These observations suggest that the conclusions of these randomized trials may be misleading.

The STAR (Stent Placement and Blood Pressure and Lipid Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery) study reported no significant difference in the primary end point of a 20% reduction in CG GFR, which occurred in 16% of patients after revascularization and 22% of patients receiving medical therapy.3 However, the present study demonstrates that CG GFR estimates are limited by poor sensitivity (0%) and poor reliability (AUC, 0.61 to 0.62) for detecting a 20% change in I-GFR. Likewise, the ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) trial failed to demonstrate a 20% change in 1/SCr after stenting compared with medical therapy.16 However, 1/SCr has poor sensitivity (16.3% to 30.2%) and poor reliability (AUC, 0.62 to 0.65) for detecting a 20% change in I-GFR. Finally, there are several ongoing multicenter prospective randomized trials comparing renal revascularization to medical therapy that are using changes in estimated GFR as primary end points,19–21 including the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial, which relies on the doubling of SCr as the primary renal end point,21 yet doubling of SCr was rare in the present study, even in patients with a >50% decline in I-GFR.

Current CKD guidelines suggest superiority of GFR estimates over SCr because of the influence of age, sex, body weight, and race on creatinine levels.18 However, in a given patient followed over several years, these variables have little impact on serial GFR estimates. The poor sensitivity of GFR estimates for detecting changes in measured GFR is attributable to their dependence on SCr, which remains constant over a wide range of GFRs.22,23 Thus, it is not surprising that changes in I-GFR may occur without corresponding changes in SCr or GFR estimates, which are fundamentally based on SCr. Our findings are further supported by a recent study demonstrating that GFR estimates were unable to detect changes in measured GFR in patients with cisplatin nephrotoxicity.24

The present study has important implications for many patients with RAS and suspected CKD. Our findings support current guidelines that recommend direct measures of GFR when precise GFR is needed clinically.18 MDRD, CKD-EPI, and CG have good sensitivity for identifying CKD. Because GFR estimates have significant limitations for identifying the stage of CKD and for assessing serial changes in GFR, more-precise methods for following GFR may be required in patients with RAS and other patients. Direct measurement of I-GFR can be efficiently and safely performed at a reasonable cost.25

Limitations

The present study was designed to evaluate the validity of GFR estimates for assessing baseline and serial changes in measured GFR in patients with RAS and was not designed to study the impact of medical therapy or renal revascularization on renal function. This analysis focused on a direct compara-
ison of estimated and measured GFR, so issues about how and why RAS was detected, whether revascularization was performed, and the presence of other comorbidities were not relevant to this study. Similarly, assessment of cardiovascular events (death, stroke, myocardial infarction, and heart failure) were beyond the scope of this study.

Importantly, sCr was measured by the modified Jaffé method, not by a standardized method directly traceable to isotope dilution mass spectrometry. Accordingly, we used the original MDRD equation rather than the modified MDRD equation, which may have resulted in minor differences (<3%) in estimated GFR by MDRD and CKD-EPI.26,27 Although only one third of patients had a body weight available within 1 month of the sCr measurement, it is important to emphasize that body weight is used only in the calculation of GFR estimates using the CG method and is not part of the MDRD or CKD-EPI GFR formulas. We used the frequency of GFR estimates within 30% of I-GFR and the frequency of correctly classifying CKD stage because these are used in current CKD practice guidelines.18 A 20% change in GFR was selected because recent randomized trials identify a 20% change as the major renal end point. Finally, the present study examined changes in renal function over long intervals (mean, 310 days) and did not assess renal function in the setting of acute kidney injury.

Conclusions
In patients with RAS, all GFR estimates are unreliable for detecting a 20% change in measured GFR, and the direction of change in estimated GFR is discordant with measured GFR in >25% of MDRD and CKD-EPI estimates and in 40% of CG estimates. Doubling of sCr is an insensitive method to detect changes in measured GFR. GFR estimates have a limited role in screening patients for CKD but should not be used as major end points in clinical trials evaluating the impact of revascularization on renal function in patients with RAS. If GFR is an important end point in clinical trials of RAS, direct measurement should be performed.

Disclosures
None.

References
In clinical practice, renal function is commonly assessed using glomerular filtration rate (GFR) estimates based on serum creatinine. Whereas several observational studies report improvement in GFR estimates in patients with renal artery stenosis after revascularization, randomized clinical trials comparing medical therapy and renal stenting have failed to demonstrate any renal benefit of revascularization. Importantly, GFR estimates have not been validated for evaluating serial changes in renal function after revascularization. Using directly measured GFR as the reference standard, this study evaluated the validity of GFR estimates for assessing serial changes in renal function in patients with renal artery stenosis and demonstrates that GFR estimates are unreliable for detecting a 20% change in measured GFR. Furthermore, correlations between percent changes in measured GFR and GFR estimates as well as the degree of agreement between serial changes in measured GFR and GFR estimates are poor. These observations suggest that conclusions of published randomized trials may be misleading and that GFR estimates should not be used as major end points in clinical trials evaluating the impact of revascularization on renal function in patients with renal artery stenosis.
Validity of Estimated Glomerular Filtration Rates for Assessment of Baseline and Serial Renal Function in Patients With Atherosclerotic Renal Artery Stenosis: Implications for Clinical Trials of Renal Revascularization
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