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Estimation of Glomerular Filtration Rate in a Pediatric Population using Non-Contrast Kidney Phase Contrast Magnetic Resonance Imaging

Alex J Barker^{1,2}, Alexander Berthussen¹, Tim Vigers^{3,4}, Michal Schafer⁵, Lorna P. Browne¹, Petter Bjornstad^{3,6}

¹Department of Radiology: Pediatric Radiology, University of Colorado, Anschutz Medical Campus, Aurora, Colorado, USA

²Department of Bioengineering, University of Colorado, Anschutz Medical Campus, Aurora, Colorado, USA

³Department of Pediatrics: Endocrinology, University of Colorado, Anschutz Medical Campus, Aurora, Colorado, USA

⁴Department of Pediatrics: Section of Biostatistics, University of Colorado School of Medicine, Aurora, CO, USA

⁵Department of Pediatrics: Cardiology, University of Colorado, Anschutz Medical Campus, Aurora, Colorado, USA

⁶Department of Medicine: Renal Diseases and Hypertension, University of Colorado, Anschutz Medical Campus, Aurora, Colorado, USA

Abstract

Background: Glomerular filtration rate (GFR) is a key measure of kidney function, but often inaccurately ascertained by serum creatinine and cystatin C in pediatrics. In this pilot trial, we evaluated the relationship between GFR derived using phase-contrast MRI (PC-MRI) biomarkers and GFR by ¹²⁵I-iothalamate clearance in youth undergoing bone marrow transplantation (BMT).

Methods: A total of twenty-one pediatric BMT candidates (8-21 years of age) were recruited for a research kidney PC-MRI. After completion of ¹²⁵I iothalamate clearance, same day PC-MRI measurements were completed of the kidney circulation without gadolinium-based contrast agent. MRI included a non-contrast balanced-SSFP triggered angiography to position ECG-gated breath-held 2D PC-MRI flow measurements (1.2×1.2×6 mm³). A multivariate model of MRI biomarkers estimating GFR (GFR-MRI) was selected using the elastic net approach.

Corresponding Author: Alex J. Barker, PhD, Associate Professor of Radiology and Bioengineering, alexander.barker@cuanschutz.edu.

Conflicts of interest: P.B. reports serving as a consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli-Lilly, LG Chemistry, Sanofi, Novo Nordisk, and Horizon Pharma. P.B. also serves on the advisory boards and/or steering committees of AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, and XORTX. The other authors have no relationships relevant to the contents of this paper to disclose.

Results: GFR-MRI variables selected by elastic net included: average heart rate during imaging (bpm), peak aorta flow below the kidney artery take-offs (ml/s), average kidney artery blood flow, average peak kidney vein blood flow, and average kidney vein blood flow (ml/s). The GFR-MRI model demonstrated strong agreement with GFR by ^{125}I iothalamate ($R^2 = 0.65$), which was stronger than what was observed with eGFR by the Full Age Spectrum and Chronic Kidney Disease in Children under 25 (CKiD U25) approaches.

Conclusion: In this pilot study, non-invasive GFR-MRI showed strong agreement with gold-standard GFR in youth scheduled for BMT. Further work is needed to evaluate whether non-contrast GFR-MRI holds promise to become a superior alternative to eGFR and GFR by clearance techniques.

Keywords

GFR; eGFR; PC-MRI; Bone Marrow Transplant; blood flow

Introduction:

Glomerular filtration rate (GFR) is central to the assessment kidney function, and is often used to diagnose kidney disease as well as determine dosing of medications cleared by the kidney [1–3]. In clinical practice, estimated GFR (eGFR) is frequently calculated by serum concentrations of endogenous filtration markers, including creatinine and cystatin C [1–3]. The pediatric equations used to calculate eGFR are derived from cohorts of young persons with chronic kidney disease, and are posited to be inaccurate at the normal-to-elevated GFR ranges, which is problematic in early disease when GFR is preserved or often elevated (hyperfiltration) [4]. The alternative is to directly measure GFR by tracking serum or urine clearance of intravenously (IV) administered exogenous filtration markers. Such measures are arduous and potentially invasive. Accordingly, use of methods to directly measure GFR remain limited to patient populations in whom the benefits of accurate ascertainment of kidney function outweigh their invasiveness, risks, and costs. Yet, several pediatric populations, including youth with obesity, diabetes mellitus, hypertension, and bone marrow transplant (BMT) recipients, are at high risk of kidney disease and may experience delay in diagnosis and treatment with inaccurate GFR ascertainment. Thus, more accurate non-invasive methods to determine GFR accurately are urgently needed.

Previous imaging studies have estimated GFR using MRI and gadolinium-based contrast media (GBCM) to model glomerulus filtration with tracer kinetic models and shown promising results [5]. However, evidence of GBCM brain deposition and the perception of non-minimal risk of nephrogenic systemic fibrosis (NSF) may cause hesitancy concerning use of gadolinium-based contrast agents in the presence of kidney disease, especially in the pediatric setting [6]. Given that kidney blood flow (KBF) is a key physiological determinant of GFR, and phase-contrast MRI (PC-MRI) is a quick noninvasive technique capable of accurately quantifying KBF (without exogenous IV contrast), we aim to assess blood flow using PC-MRI measurements to estimate GFR in children being evaluated for bone marrow transplant. Young persons scheduled to receive a BMT undergo GFR ascertainment by ^{125}I -iothalamate clearance at our hospital and thus represent an ideal participant population to test the performance of PC-MRI to estimate GFR. We hypothesized in this pilot and

feasibility trial that a non-contrast agent approach using PC-MRI biomarkers would strongly associate with GFR by ^{125}I -iothalamate clearance in young BMT candidates.

Methods:

A total of twenty-one pediatric BMT candidates were prospectively recruited for a research kidney MRI. Participants 8 to 21 years of age who were scheduled to undergo a BMT and an ^{125}I iothalamate clearance study to quantify GFR were eligible to enroll in the study. Before the MRI, fasting urine was collected to assess albumin-to-creatinine ratio (ACR) and blood to serum creatinine and cystatin C. Serum creatinine and cystatin C were used to estimate GFR by Full Age Spectrum (FAS), and Chronic Kidney Disease in Children under 25 (CKiD U25) equations [7]. All laboratory assays were performed by the University of Colorado CTSC Core Labs. Creatinine was assessed enzymatically (Beckman Coulter, California, US) and cystatin C immunoturbidimetrically (Kamiya Biomedical, Washington, US). A Siemens Nephelometry instrument was used to measure urine microalbumin (Siemens Healthineers, Erlangen, Germany).

After completion of ^{125}I iothalamate clearance, same day PC-MRI measurements were completed of the kidney circulation. MRI included balanced-SSFP TRiggered ANgiography non-Contrast Enhanced (B-TRANCE) imaging to position ECG-gated breath-held 2D PC-MRI flow measurements ($1.2 \times 1.2 \times 6 \text{ mm}^3$). PC-MRI was positioned orthogonal to the left and right kidney artery at the takeoff of the descending aorta. When venous kidney flow was visible, additional images were acquired of the venous return. In all cases, velocity sensitivity ($v_{\text{enc}} \approx 100 \text{ cm/s}$) was adjusted to avoid velocity aliasing. Bilateral, time-resolved arterial and venous KBF were measured using region of interests drawn in Circle CVI42 (Calgary). Right, left, and total arterial and venous net flow, peak flow, and peak velocity were computed. Total bilateral blood flow was computed as the sum of the left and right kidney vessels.

Statistical Analysis:

A final multivariate model was selected using the elastic net approach with the shrinkage parameters lambda and alpha selected using leave one out cross-validation (R packages glmnet and caret) [8]. Lambda and alpha were chosen to produce the most parsimonious model with root mean squared error (RMSE) within 1 standard error of the minimum obtained during cross-validation. Rather than using a stepwise approach based on statistical significance, elastic net model selection is based on minimizing prediction error. After model selection with elastic net, simple linear models were fit using the selected markers as predictors. MRI models to estimate GFR were compared to eGFR calculations by serum creatinine and cystatin C based on the coefficient of determination (R^2) between predicted values and gold standard GFR measurement (Figure 1).

MRI variables selected by the elastic net included average heart rate during imaging (bpm), peak aorta flow below the kidney artery take-offs (ml/s), average kidney artery blood flow, average peak kidney vein blood flow, and average kidney vein blood flow (ml/s). Average kidney artery blood flow was calculated by summing the average superior and inferior kidney artery blood flow (if present) on the right and left sides and taking the mean of the

two sides. Average peak kidney vein blood flow and average kidney vein blood flow were calculated similarly.

Results:

Twenty of twenty-one research participants completed the study protocol. One participant was excluded due to claustrophobia on commencement of the research MRI and an inability to complete the scan. Supplementary Table 1 summarizes the participant characteristics. Briefly, 43% of the participants were female with a median age of 15 years, median GFR-iothalamate of 136 ml/min. None of the participants exhibited elevated albuminuria.

Figure 1 shows the agreements among GFR-iothalamate, eGFR and GFR-MRI. The agreements between BSA-indexed and non BSA-indexed GFR-iothalamate and GFR-MRI models were superior to those observed with eGFR by CKiD U25 and FAS. For example, the BSA indexed R^2 correlations to GFR-iothalamate for eGFR by CKiD U25 and FAS were 0.390 and 0.299, respectively, as compared to $R^2=0.538$ for the GFR-MRI model. Additionally, the non-BSA indexed R^2 was 0.654 for the GFR-MRI model.

Discussion:

GFR is vital to the assessment of kidney function, and is used to define and stage chronic kidney disease (CKD) [1–3]. Even with improved methods to estimate GFR, the use of endogenous filtration markers lack precision and accuracy before CKD stage 3 [9–13]. Racial disparities in equation performance have also been recently highlighted [12, 14]. Furthermore, longitudinal changes in estimated GFR may not reflect changes in measured GFR [15]. These shortcomings are of particular concern in pediatric populations at high risk for kidney disease, as the disconnect between eGFR and measured GFR can cause misclassification of early kidney disease as well as flawed longitudinal trajectories of kidney function [16].

Previous MRI-based studies have investigated GBCM-based tracer kinetic models with a two-compartment model and compelling correlations to gold standard GFR measurements were found ($R^2 = 0.97$) [5]. However, these studies require exogenous agents with non-minimal risk surrounding GBCM brain deposition and concerns surrounding NSF in individuals with impaired kidneys [6]. Here we show a non-contrast method which better predicts GFR than eGFR approaches using creatinine and cystatin C.

This pilot and feasibility study has several constraints worth mentioning, including the small sample size and the lack of test-retest reliability of the GFR-MRI. Therefore, the data should be considered hypothesis generating. Strengths of the study include gold-standard measurements of GFR by ^{125}I -iothalamate clearance. Future studies will need to consider the cost/benefit of GFR-MRI as compared to laboratory-based approaches.

In conclusion, the poor performance of eGFR by creatinine and cystatin C in youth is problematic because inaccurate estimates of kidney function can lead to inconsistent treatment, intervention, and increased costs. Here, we found GFR estimated by the MRI model correlated strongly with GFR by iothalamate, the gold standard. However, GFR

determined by clearance techniques are impractical and too invasive for widespread clinical use. Thus, non-invasive and, ideally non-GBCM, methods are needed that can accurately detect changes in GFR where interventions may be the best option to preserve kidney structure and function. Although data from this pilot and feasibility study should be limited to hypothesis generating, we contend that GFR-MRI represents a technological advancement of clinical importance and holds promise to become a superior alternative to eGFR and GFR by clearance techniques in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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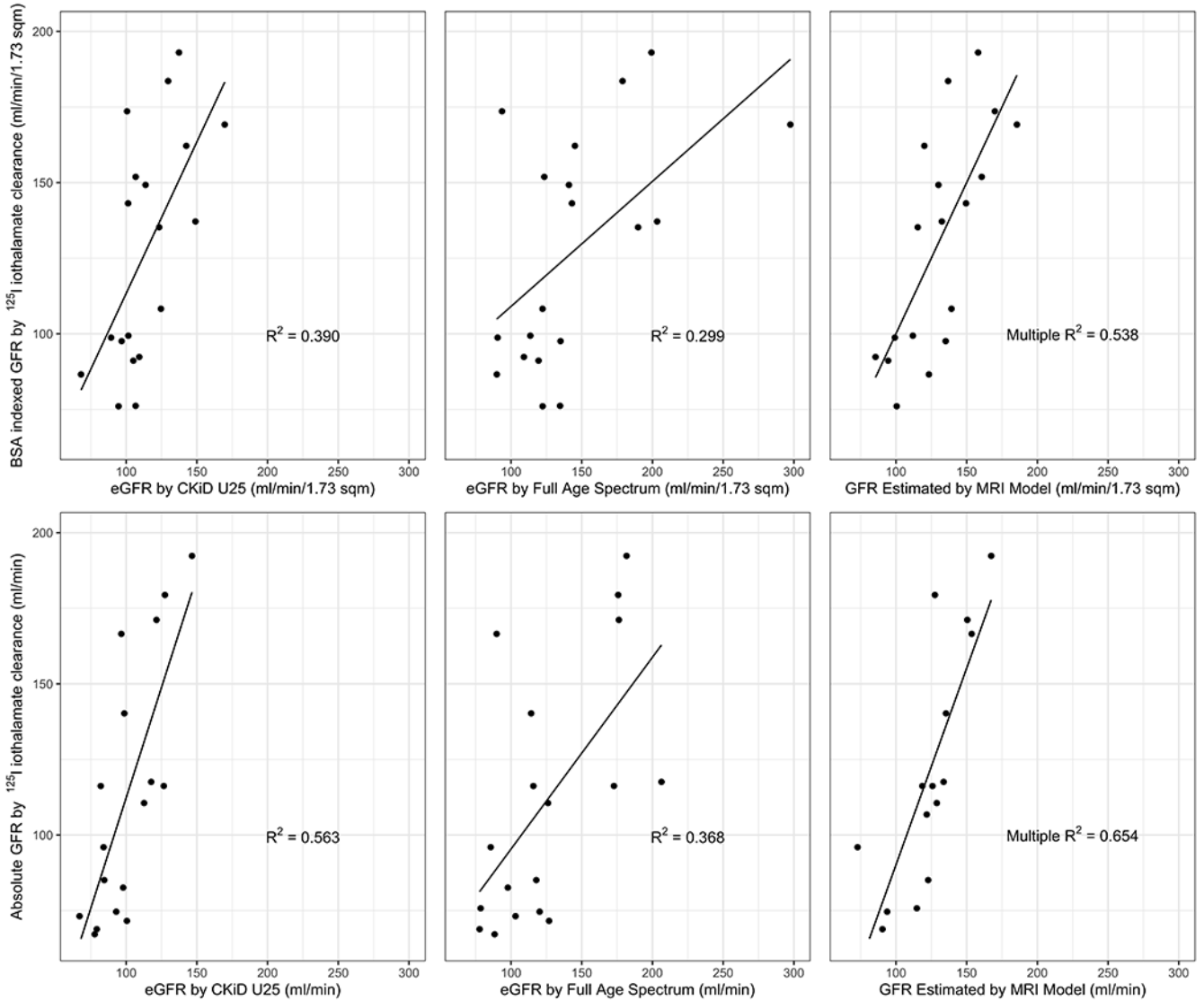


Figure 1.

Agreements among iothalamate-based GFR, eGFR and GFR-MRI. Correlations between iothalamate based GFR and estimated GFR (BSA indexed and non-indexed) are shown, as well as GFR estimated by MRI model. The MRI model predicting indexed iothalamate based GFR included average heart rate, peak aorta flow below the kidney artery take-offs, average kidney artery blood flow, average peak kidney vein blood flow, age, and sex. The MRI model predicting absolute iothalamate based GFR includes average heart rate, peak aorta flow below kidney artery take-offs, average kidney vein blood flow, average peak kidney vein blood flow, age, and sex. Note: CKiD U25 and FAS were calculated according to Pottel et al., NDT 2015, PMID: 26932693.