Kidney Transplant Donor Glomerular Filtration Rate by Iohexol Clearance During Computerized Tomographic Angiography of the Kidneys

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ABSTRACT

Background. Pre-transplantation living-donor kidney function determines remaining donor kidney function and significantly affects post-transplantation allograft function in the recipient. Few transplantation centers perform donor kidney function measurement owing to patient burden. A simplified method of glomerular filtration rate (GFR) measurement after angiographic procedures may facilitate more precise measurement of donor kidney function.

Methods. We evaluated the agreement between a simplified method of GFR measurement after renal computerized tomographic (CT) angiography (index GFR, 100 mL iohexol [350 mg/mL iodine]) and the reference GFR measurement with the use of iodinated radiocontrast media (5 mL bolus of iohexol [300 mg/mL iodine]) among 19 potential living kidney transplant donors. The 24-hour creatinine clearance and GFR estimation equations were additionally examined. Kidney lengths and total and segmented cortical kidney volumes were also measured.

Results. The index CT angiography GFR performed best with respect to the reference GFR with minimal bias (mean difference, −4 mL/min/1.73 m^2), good precision (SD of the difference, 9.8 mL/min/1.73 m^2), coefficient of determination (R^2) of 0.74, narrow mean coefficient of variation (5% [range 1%−15%]), and high accuracy, with 100% of the values for the index test within 30% of the reference test. The 24-hour urine creatinine clearance values performed poorly. Kidney volumes and length did not significantly correlate with measured GFR.

Conclusions. The CT angiographic GFR measurement could be a useful and more convenient method of donor kidney function evaluation and maintains minimal bias, high precision, and accuracy compared with the reference GFR measurement.

PROPER DETERMINATION of donor kidney function ensures the longevity of post-transplantation living-donor kidney function and recipient graft function. The 24-hour urine creatinine clearance evaluation is the most common method of donor kidney function assessment[1] rather than the more cumbersome direct GFR measurement which entails repeated phlebotomy and/or exposure to radioisotopes. Nonradioactive iso-osmolar iodinated contrast media clearance is an alternative reference GFR measurement[2,3] that can be performed during routine angiography, minimizing patient burden. Iodinated contrast media clearance during angiography has high correlation with simultaneously measured GFR by ^{51}Cr-EDTA plasma

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clearance ($R^2 = 0.89$)[4] or inulin clearance ($R^2 = 0.96$)[5] despite the usual day-to-day variation of GFR.[6]

Transplant donors commonly undergo computerized tomographic (CT) angiography to characterize the renal anatomy before surgery, which allows for the opportunity to measure GFR via iodinated contrast media clearance. We examined the agreement between GFR measurement after CT angiography of the kidneys and the reference standard GFR measurement[3] with the use of iodinated radiocontrast media among potential living kidney transplant donors. Kidney size was also evaluated with respect to the reference GFR measurement.

METHODS

Potential living kidney transplant donors undergoing scheduled outpatient CT angiography of the kidneys were identified from Rhode Island Hospital from 2009 to 2011 for GFR measurement during angiography. Human subjects protection approval was granted by the Lifespan Institutional Review Board. Adults with contrast dye allergy, recent contrast dye exposure (<1 wk), hemodynamic instability, or excessive rise in creatinine with coefficient of variation (CV; SD divided by the mean of the 2 measurements) >20% were excluded from consideration.

Demographic data (age, sex, race, height, and weight), comorbid conditions, medications, creatinine, 24-hour urine creatinine clearance, and GFR estimated by the Modification of Diet in Renal Disease (MDRD) formula[7] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[8] were obtained. Patient characteristics were assessed with the use of mean ± SD and median for continuous variables and percentages for categoric variables.

During helical CT angiography of the kidneys for living-donor kidney transplantation on the same 64-detector-row CT scanner (VCT; GE Medical Systems), post-contrast imaging was obtained in the corticomedullary phase after 100 mL iohexol (350 mg/mL iodine) was administered over 0.42 minutes (4 mL/s) in each subject. Contrast injection was initiated with the use of smart prep with region of interest placed on the aorta at the level of the proximal celiac artery with a trigger enhancement threshold of +100 Hounsfield units (HU). Then plasma iohexol concentrations were assessed at 2, 3, and 4 hours after the last contrast dose administration during scheduled CT angiography. Approximately 2 weeks after the CT angiography GFR measurement, the reference standard GFR measurement was performed similarly with the use of a 5 mL bolus of iohexol (300 mg/mL iodine) given over 2 minutes (with the exception of 1 patient who received 5 mL 350 mg/mL iodine).

Segmented cortical volumes were calculated on the CT workstation from the CT data with the use of manual thresholding with a value that differentiated enhancing cortex from the medulla and collecting system (average 118 HU, range 88–173 HU). Results of each kidney were summed for calculation of segmented cortical volumes for each patient. Renal lengths were also measured as the greatest bipolar dimension obtained from the 3-dimensional volume-rendered images.

Standardized serum creatinine was measured with the use of the Roche enzymatic method, and plasma iohexol concentrations were quantified with the use of high-performance liquid chromatography at the University of Minnesota Physicians Outreach Laboratories, Minneapolis. Iohexol clearance was analyzed by the methods described by Brochner-Mortensen.[9]

The index angiography GFR was evaluated with respect to the reference standard GFR, examining bias, precision, and accuracy. Bias was assessed with the use of a modified Bland-Altman test (difference between the index and reference test vs the reference tests). Precision was determined by the SD of the difference between the index and reference test, as well as by the coefficient of determination (R^2) of the index angiography GFR with respect to the reference standard GFR. Additionally, the mean CV was calculated for the index test compared with the reference test. Accuracy was assessed by comparison of the index GFR measurement with the reference standard GFR measurement using the equation: (predicted value − true value) × 100/standard iohexol measurement. Finally, correlation of volumetric (total and segmented cortical) and length (sum and average of both kidneys) measurements with the reference measured GFR was assessed with the use of the coefficient of determination (R^2).

RESULTS

Nineteen potential living kidney transplantation donors undergoing scheduled outpatient renal CT angiography were selected for GFR measurement. Two patients failed to complete the study owing to loss of follow-up and blood specimen collection error. In the remaining 17, mean age was 47 (range 29–64) years; 75% were male; the majority of subjects (76%) were White and the others Black, Hispanic, and Asian. Average height and weight were 67 ± 4 in and 175 ± 34 lb, respectively. Mean serum creatinine concentration was 0.87 ± 0.15 (range 0.60–1.14) mg/dL and

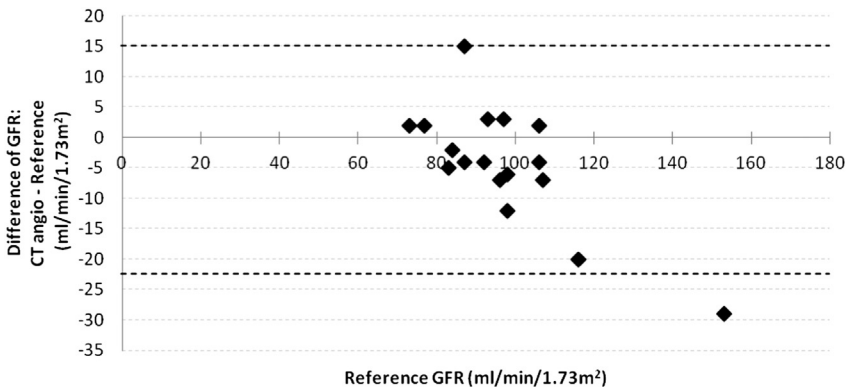

Fig 1. Reference glomerular filtration rate (GFR) measurement versus difference between index angiography GFR and reference GFR measurements.

Table 1. Agreement Between the Index and Reference GFR

Index GFR	Bias	Precision	CV, %	Accuracy	
				% Within 30%	% Within 50%
CT angio-mGFR	−4.00	9.80	5.17	100.00	100.00
CKD-EPI eGFR	−6.00	12.67	7.43	100.00	100.00
MDRD eGFR	−11.60	15.03	11.47	94.11	100.00
24 h urine CrCl	31.00	30.00	21.30	47.06	76.47

Abbreviations: angio, angiography; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CrCl, creatinine clearance; CT, computerized tomographic; CV; coefficient of variation; eGFR, estimated GFR; GFR, glomerular filtration rate; mGFR, measured GFR; MDRD, Modification of Diet in Renal Disease.

mean estimated GFR (eGFR) by the CKD-EP) estimation equation was 92 ± 14 (range 70–120) mL/min/1.73 m^2.

Agreement of the CT angiography GFR (index) to the reference standard GFR (5 mL iohexol plasma clearance) was assessed. Figure 1 shows the modified Bland-Altman plot. Bias was minimal (−4 mL/min/1.73 m^2) and precision was high (9.8 mL/min/1.73 m^2 [95% limit of agreement −23 to 15 mL/min/1.73 m^2]), as listed in Table 1. The coefficient of determination (R^2) of the index CT angiography GFR with respect to the reference standard GFR was 0.74 ($P < .0001$) as shown in Fig 2. Mean CV was only 5% (range 1%–15%) for the index test compared with the reference test. Regarding accuracy, 100% of values for the index CT angiography GFR were within 30% of the reference test. Reanalysis excluding 1 outlier (measured GFR of 153 mL/min/1.73 m^2) was essentially unchanged. In addition, preangiography GFR estimation equations (CKD-EPI, MDRD) underestimated GFR and the 24-hour urine creatinine clearance overestimated GFR with poor performance (Table 1; Fig 2).

Neither length nor volumetric assessment of the donor kidneys correlated significantly with measured GFR. The coefficient of determination (R^2) for total renal volume was only 0.009. Correlation with reference GFR for kidney length measured in sum and average of both kidneys was slightly better ($R^2 = 0.063$). Segmented cortical volumes best correlated with the reference measured GFR, with an R^2 of 0.216, where this association was nearly significant with a P value of .06.

DISCUSSION

Donor kidney function determines residual donor kidney function and recipient kidney function after living-donor kidney transplantation.[10] Unfortunately, precise measurement of the GFR traditionally requires radioisotopes, repeated phlebotomy, and urine collection, which is cumbersome and time consuming. The commonly used GFR estimation equations tend to underestimate GFR in the transplantation donor population, with poor precision by coefficient of determination ($R^2 = 0.1$–0.4), excessive absolute bias (10–20 mL/min/1.73 m^2), and accuracy of only 55%–89% within 30% of measured GFR[11–15]; all of which were consistent with our results.

The proportion of centers that use GFR measurement for donor kidney function evaluation is <10%. Most transplantation centers rely on 24-hour urine creatinine clearance with adjunctive creatinine-based GFR estimation equations as the primary method of GFR evaluation.[1] Overestimation of GFR when using the urinary creatinine clearance may put donors at risk for development of CKD in addition to the increased risk of allograft failure in the recipient, whereas underestimation of GFR by the estimation equations may exclude healthy potential donors.

Donor Measured GFR

Few studies have looked at simplifying GFR measurement methods which could facilitate more accurate GFR assessments. A recent study using detection of external whole tissue radioactivity after single intravenous injection of ^{99}technecium-DTPA highly correlated ($R^2 = 0.97$) with iothalamate clearance, where patients were required to spend <60 minutes to complete the GFR measurement. However, this method requires the use of radioisotope

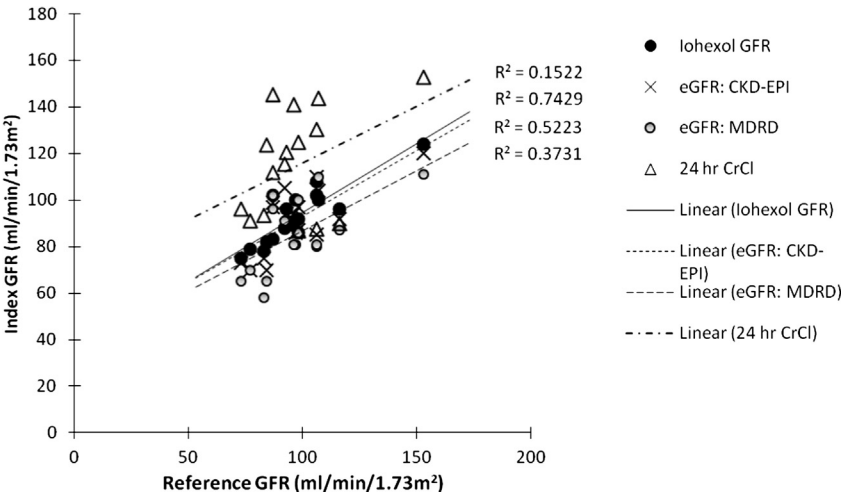

Fig 2. Comparison of transplant donor glomerular filtration rate (GFR) measurement methods by coefficient of determination.

administration and specialized equipment that is not clinically available currently.[16] Clearances of nonradioactive substances such as iodinated contrast agents during routine CT imaging or angiographic studies have shown good correlation with measured GFR in the nontransplantation population.[4–6,17] GFR evaluation after CT angiography is a highly consistent method using uniform doses of contrast over the same time interval; and it avoids unnecessary additional contrast dye exposure, procedures, and additional office visits. In potential transplant donors, we have found that GFR measurement through iohexol clearance performed at the time of CT angiography of the kidneys is a simplified method of GFR evaluation that had minimal bias and high accuracy and precision (Table 1). The CV of this method was essentially no different than intraindividual CV (range 5.6%–8.4%) observed for repeated GFR measurements in one individual.[18–20] Not surprisingly, the 24-hour urine creatinine clearance most poorly estimated GFR. Of the GFR estimation equations, the CKD-EPI formula was the least biased and most accurate although it tended to underestimate GFR. Many centers continue to use the urinary creatinine clearance during donor evaluation as the primary GFR assessment. However, GFR measurement with the use of CT angiography would allow for a more measured approach to donor evaluation, particularly in patients with conflicting GFR assessments or borderline candidates who require greater scrutiny in donor assessment.

The assay for iohexol clearance is available in nonresearch settings in selected laboratories and is relatively affordable (~$100–$200/patient); however, it requires additional labor costs. Possible sources of error include the high iohexol dose and iodinated contrast media–related renal arteriolar constriction. However, the standardized contrast media administration during angiography allows for uniform and consistent GFR measurements. The present sample size, though small, was sufficient to demonstrate the accuracy and precision of the GFR measurement with the use of CT angiography in a potential renal transplant donor population.

Donor Kidney Size

In addition to measured pre-transplantation GFR, kidney size (measured as length, weight, or volume) is often cited as a predictive factor for allograft function.[21] Donor kidney size has been shown to correlate with donor kidney function[22] and recipient allograft function.[23,24] The ideal measure of kidney size has not been determined, but recent publications seem to favor total kidney volume, particularly in live-donor transplantation.[23] The volumetric measurement of the kidneys has been shown to be a more useful predictor of recipient kidney function at 1 year compared with donor creatinine clearance, body surface area, or body mass index in the live-donor kidney transplantation population.[23] On the other hand, in a study using ^{99}Tc-DTPA GFR measurement as the reference GFR, ultrasound examination of kidney length correlated best with recipient and donor function, compared with total volume.[21] Threshold graft lengths, resistive index levels, and end-diastolic velocity also have been predictive of recipient renal outcomes.[24] We found that segmented cortical volume measurements seemed to best correlate with measured GFR of donors compared with total volume or length; however, this was not statistically significant. We did not find significant correlation of kidney volume or length with donor kidney function, possibly owing to our small sample size. Larger studies to correlate segmented cortical volume with donor residual and recipient renal function would be valuable to further understand the effect of donor factors on post-nephrectomy donor outcomes and recipient kidney function.

In summary, GFR measurement with the use of plasma iohexol clearance during routine renal CT angiography of healthy potential kidney donors was demonstrated to have minimal bias and to be precise and accurate compared with the reference GFR measurement. The renal CT angiographic GFR measurement is potentially a useful and more convenient method of donor kidney function evaluation.

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