Serum creatinine can be used as a surrogate for glomerular filtration rate in single renal unit models

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GOFRIT ON, ORVIETO MA, ZORN KC, STEINBERG GD, ZAGAJA GP, SHALHAV AL. Serum creatinine can be used as a surrogate for glomerular filtration rate in single renal unit models. The Canadian Journal of Urology. 2009;16(1):4452-4457.

Background and purpose: *Single renal unit models are invaluable for studies in renal physiology, transplantation and response to ischemic injury. Glomerular filtration rate (GFR) is commonly used for evaluation of renal function. Measuring the GFR involves relatively complicated and expensive systems. In this study we determined whether serum creatinine (Scr) can predict the GFR in this model.*
Materials and methods: *Right laparoscopic nephrectomy was performed in 46 female pigs weighing 25 kg-30 kg. Twelve days later the left kidney was exposed to various periods of warm ischemia (30, 60, 90, and 120 minutes). Scr and GFR (using the iohexol clearance method) were determined preoperatively and at postoperative days 1, 3, 8, 15, 22 and 29. A total of 244 pairs of Scr and GFR values were analyzed to determine a formula for predicting GFR (pGFR) from Scr.*
Results: *Scr range was 1.2 mg/dl -29 mg/dl and GFR range was 1.8 ml/min -180.5 ml/min. The empiric formula deduced from the database for calculating pGFR from Scr was: pGFR = (217 divided by Scr) minus 0.2. pGFR correlated well with the actual GFR (R^2 = 0.85). The graphs for pGFR were almost indistinguishable from the graphs for actual GFR in every single animal. The results and conclusions of the experiments using either actual or predicted GFR were identical.*
Conclusions: *We conclude that in a single renal unit porcine model using ischemia as the insult to the kidney, expensive actual measurements of GFR can be reliably replaced by Scr based calculated GFR.*

Key Words: glomerular filtration rate, single renal unit model, serum creatinine

Introduction

Glomerular filtration rate (GFR) is the best overall index of renal function. Measuring the GFR however, is not easy. The clearance of inulin (Cin), a natural fructose polymer that is unmetabolized, filtered but neither secreted nor reabsorbed is considered the "gold standard" for this purpose.[1] Although accurate, measuring Cin requires continuous intravenous infusion, urine collection, multiple blood sampling and a difficult chemical assay. Therefore measuring Cin is impractical in most settings. Radioactive methods for determination of GFR using either ^{99m}Tc-labaled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) or ^{51}Cr-labeled Ethylenediaminetetraaceric acid (^{51}Cr-EDTA) also provide accurate estimates of the GFR but require the use of radioactive substances and specialized monitoring devices.[2,3] The modern

Accepted for publication October 2008

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method for measuring the GFR employs the use of the non-ionic, low osmolarity radiographic contrast iohexol (Omnipaque). This agent is not bound to plasma proteins, is freely filtered in the glomerulus, neither reabsorbed nor secreted or metabolized and has a negligible extrarenal excretion. For determination of GFR, iohexol is injected intravenously and its serum levels are determined using x-ray fluorescence analysis equipment.[4] No urinary collection is required. The accuracy of the iohexol estimate of GFR was verified against renal Cin and ^{51}Cr-EDTA, and was found virtually identical even when GFR is reduced.[4-7]

Although easier than inulin, the iohexol method still requires injection of the substance, multiple blood samplings (usually through externalized or internalized venous access port), and a specific instrument for determining iohexol levels. If a simple endogenous marker could be used to estimate of GFR then experimental studies in renal physiology would be made easier and cheaper.

In clinical practice, serum creatinine (Scr) and the creatinine clearance (Ccr) are the most frequently used surrogates for GFR. Creatinine is far from being the perfect filtration marker. Its metabolism is dependent on muscle mass and diet; and although freely filtered at the glomerulus, a substantial fraction of creatinine excreted by the kidney is the result of proximal tubular secretion. In low rates of urine flow, creatinine is also reabsorbed from the lumen to the blood by passive back diffusion.[1] Scr remains normal or slightly elevated and Ccr remains normal or slightly depressed in membranous glomerulonephritis, transplant glomerulopathy, and SLE despite a marked decrease in GFR.[8,9] The disparity between GFR and creatinine based estimates of GFR increases especially in proteinuric glomerular disorders as creatinine is hypersecreted progressively by remnant renal tubules as the disease worsens.[8-10]

Are these observations made in patients with diabetic or immune glomerlopathies implying also to experimental models of renal insufficiency in which the main insult is ischemia? In this study we determined whether the simple measurement of Scr can be used as a surrogate for a directly measured GFR in an experimental porcinemodel of renal failure.

Materials and methods

Two experiments were designed to test the effect of renal warm ischemia in a single renal unit porcine model; all experiments were approved by the institutional animal care and use committee. A total of 46 female farm pigs weighting 25 kg-30 kg were anesthetized and underwent transperitoneal laparoscopic right nephrectomy and the placement of internalized tunneled jugular venous access port (Titanium Soloport Intech Laboratories, Plymouth Meeting, Pennsylvania) to allow iohexol injection and blood sampling. In both experiments, the second kidney operation was performed 12 days after the initial nephrectomy.

In the first experiment, 26 pigs were exposed to warm ischemia of 30, 60 and 90 minutes either by laparoscopic or by open clamping the renal hilum.[11] In the second experiment, 20 pigs were exposed to 120 minutes of warm ischemia again, either by laparoscopic or by open clamping the renal hilum.[12] Creatinine and GFR determinations were done using the same methodology.

Determination of serum creatinine was performed using the routine Jaffé method on an automatic multichannel analyzer. GFR was measured using the plasma iohexol clearance method.[7] Each pig received intravenous injection of 10 ml iohexol (Omnipaque180, Winthrop Pharmaceutical Co., Dallas, TX; iodine concentration 180 mg/ml). Blood samples were obtained 3 and 4 hours after iohexol injection (a third blood sample was obtained 8 hours after injection if calculated GFR was found lower than 30 ml/min). Plasma iodide content was measured using the x-ray fluorescent method (Renalyzer, PROVALID AB, Lund Sweden). GFR was calculated using the slope intercept technique.[7]

Scr and GFR were determined preoperatively and on postoperative days 1, 3, 8, 15, 22, and 29 in the first experiment and postoperative days 1,3, 8, and 15 in the second experiment. Statistical analysis was performed using the JMP 5.01 software package (SAS Campus Drive, Cary, NC). The formula for calculating GFR was deduced by the software using a standard least of square analysis.

Results

The range of GFR found in the experiments was from 1.8 ml/min -180.5 ml/min, and the range of Scr was 1.2 mg/dl -29.9 mg/dl. A total of 244 pairs of measurements were evaluated (145 from the first experiment and 99 from the second experiment). The Scr-GFR plot showed the typical hyperbolic association, Figure 1. The empiric formula deduced from the database for predicting GFR from Scr was:

$$pGFR = \frac{217}{Scr} - 0.2$$

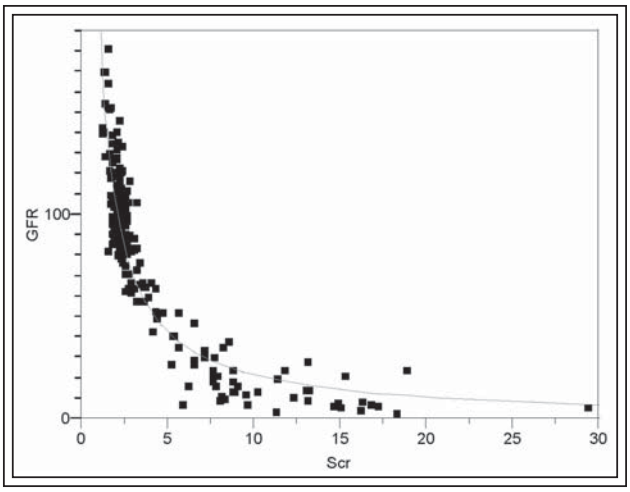

Figure 1. Scr-GFR plot showing the hyperbolic relationship between Scr and the GFR. The red curve is the fit reciprocal line.

The formula was tested against the actual iohexol measured GFR using the standard least square model and gave a good prediction of the GFR ($R^2 = 0.85$). Figure 2 is a leverage plot showing the regression line and 95% confidence intervals. The confidence curves cross the horizontal line (where the hypothesized value of the parameter effect is constrained to zero), indicating that the association between the predicted and actual GFRs is significant ($p < 0.0001$). Figure 3 is a residual by predicted plot showing that the models' predictions were most accurate at GFR levels < 90 ml/min.

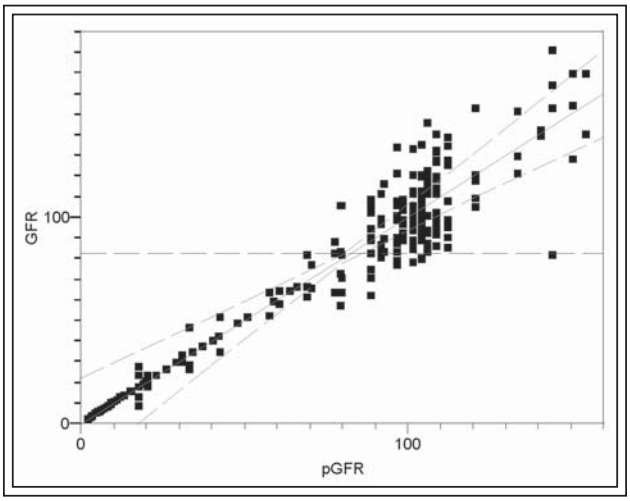

Figure 2. Leverage plot for predicted GFR-actual GFR. The regression line (solid line) and the 95% confidence lines (broken lines) are shown. The blue horizontal line is the hypothesized value where the parameter effect is constrained to zero.

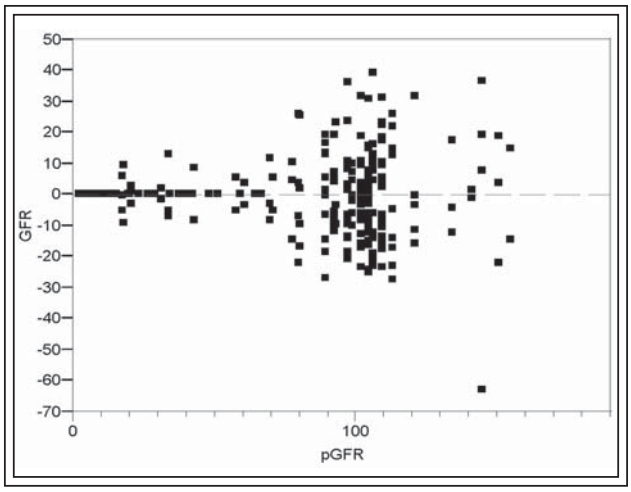

Figure 3. Predicted GFR-actual GFR residual by predicted plot showing that the models prediction is best at GFR levels < 90 ml/min.

The results of the two experiments were reanalyzed using the pGFR, Figures 4 and 5. The curves for the predicted and actual GFR were almost identical in most animals. Minor differences were noted between the actual and predicted GFRs, particularly at preoperative GFR values higher than 120 ml/min. Differences > 10% between GFR and pGFR in preoperative GFR levels were found in 6/46 animals (13%). Using pGFR as surrogate for GFR did not change the final conclusions of both experiments.

Pigs' weight varied only less than 5% the experiment. Incorporating the weight of the pig, or calculating GFR ratios comparing the preoperative to postoperative Scr (preoperative Scr/postoperative Scr on day X) did not give better results compared to the simple formula used.

Discussion

The single renal unit model is invaluable for studies in renal physiology, transplantation and response to injuries.[13,14] In the field of oncologic surgery, there is renewed interest in this model since the introduction of laparoscopic partial nephrectomy techniques using warm ischemia.[15] Questions regarding renal tissue preservation during warm and cold ischemia are frequently studied using this model.[11,12] Evaluating residual renal function in this model almost always implies assessment of the GFR. The iohexol method is the preferred method of direct measurement of GFR. This method although accurate, is time consuming, expensive, and in most cases requires a venous access port.[4-7]

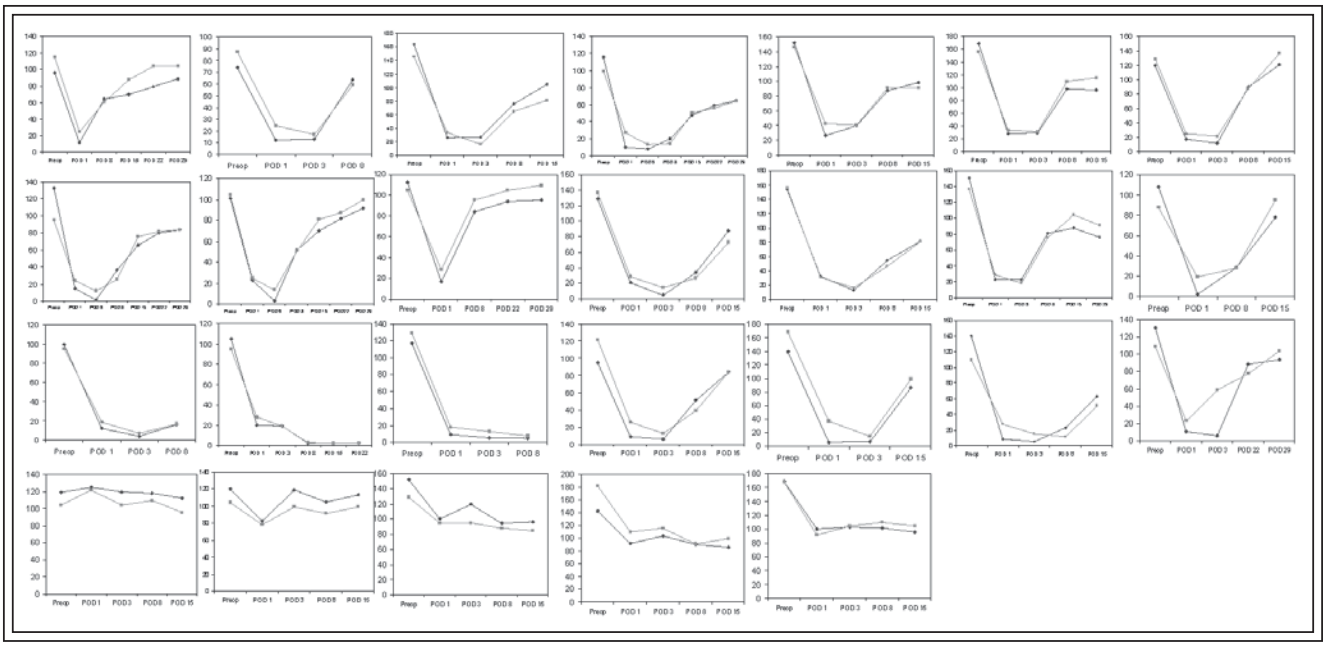

Figure 4. Results of the first experiment. Each curve represents one pig. The predicted GFR is the gray line and the actual GFR the black.

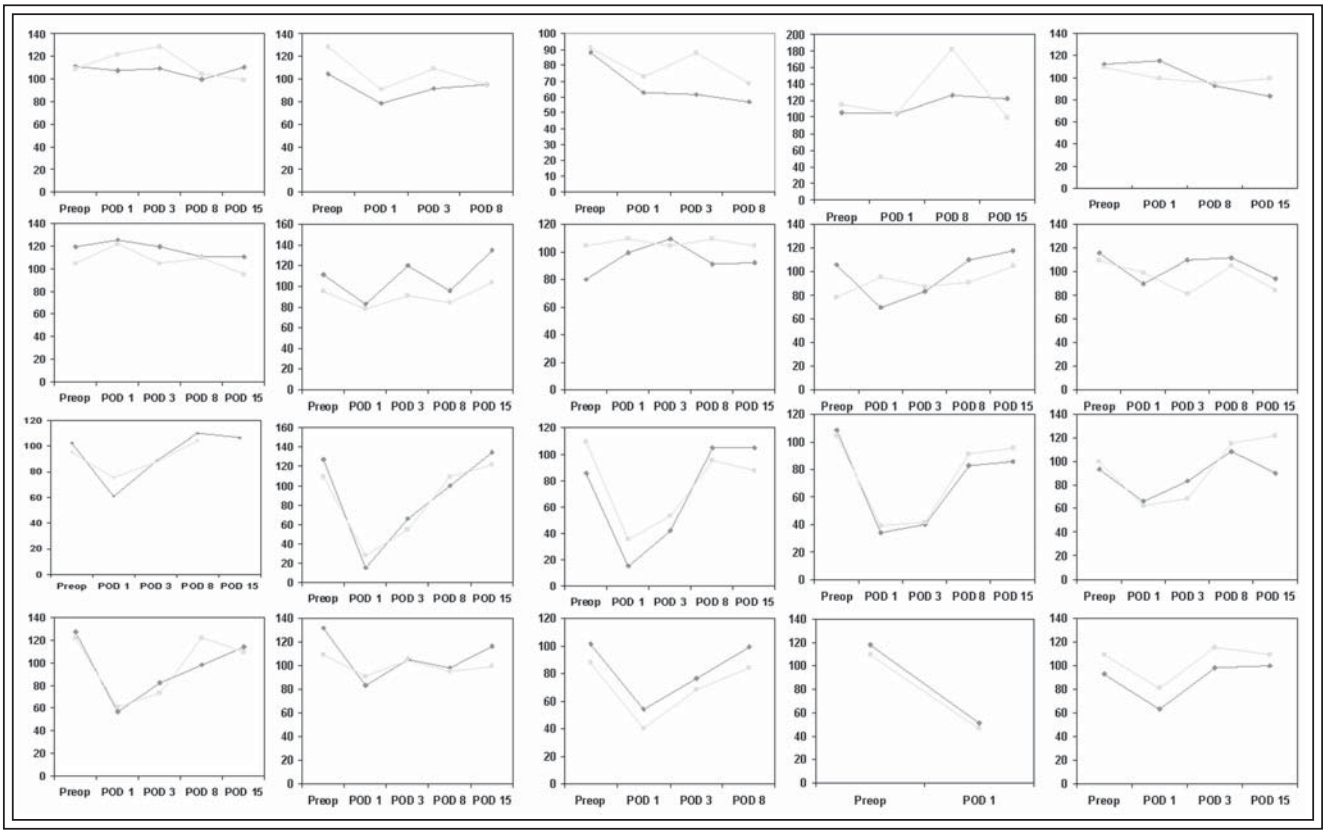

Figure 5. Results of the second experiment. Each curve represents one pig. The predicted GFR is the gray line and the actual GFR the black.

Using serum creatinine for evaluation of GFR would eliminate the need for injecting iohexol, for multiple blood samplings, and for the special equipment required for measuring iohexol levels. A commercial, cheap, and well controlled method to determine Scr is available in every institution, but can it be used for accurate evaluation of GFR?

In this study, using a single renal unit porcine model, we compared the results of the iohexol determined GFR to the Scr predicted GFR. We demonstrated that when renal ischemia occurs in a single renal unit model, Scr can be used with the aid of a simple formula (pGFR = (217divided by Scr) minus 0.2), as a surrogate for GFR. The plotted pGFR curves almost duplicated the actual GFR curves for all 46 animals studied, Figures 4 and 5. The predictions were precise over a wide range of creatinine levels (1.2 mg/dl -29 mg/dl), and were most accurate when GFR was less than 90 ml/min.

These findings are contradictory to many previous observations showing a discrepancy between Scr based estimations of GFR and the actual GFR, particularly when GFR is low.[8-10] Differences in the mechanism leading to renal failure explain the contradiction.

In renal ischemia, as in the animal model employed here, the proximal tubule is the predominant site of injury- a condition often termed acute tubular necrosis (ATN). The proximal tubule (especially its pars recta), along with the medullary thick ascending limb (mTAL) segment of the loop of Henle are the nephron's most susceptible segments to ischemia. This is due to their high ATP requirements for active solute transport and the location in the outer medulla that is more hypoxic due to regional differences in blood flow. The reduction in GFR, also found in ATN induced by renal ischemia, is secondary to mesangial cell contraction (reducing the glomerular ultrafiltration coefficient-K_f), to intrarenal vasoconstriction, tubule obstruction and back leakage. The final product is simultaneous decrease in both glomerular and tubular functions.[16] On the contrary, primary glomerular disorders were the leading cause of renal failures in the studies reporting on the discrepancy between the Scr based estimates and the GFR.[8-10] In these disorders tubular function is often preserved more than glomerular function. As GFR falls, tubular secretion of creatinine increases. As a result Scr may remain within the normal range, despite marked impairment in renal structure and function.[1] In these conditions Scr is not an adequate surrogate for GFR.

Therefore, the conclusions of this manuscript should be limited to models involving renal ischemic damage only. In other models of renal failure, the accuracy of the predictive formula should be verified.

In clinical work Ccr is often deduced from the value of Scr value using the Cockcroft and Gault formula.[17] In addition to Scr, the formula also incorporates patient's age weight and gender. In the current experiments using female pigs only, of similar age and weight, Scr was the only influencing parameter.

Conclusions

We have demonstrated that in the single renal unit model using ischemic injury as the insult to the kidney, expensive actual measurements of GFR can be reliably replaced by serum creatinine based calculated GFR. The formula is: pGFR = (217divided by Scr) minus 0.2. This conclusion is currently limited to ischemic models of renal failure. □

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EDITORIAL COMMENT

In this article, "Can serum creatinine be used as a surrogate for glomerular filtration rate in single renal unit models?" Gofrit and colleagues derive an estimate of GFR in an ischemic model of acute renal failure in pigs with unilateral nephrectomy. The authors rightly note that the more accurate measures of GFR are not simple while use of creatinine is limited by accuracy due to the variable secretion of this molecule by the proximal tubule. Despite these variables, the use of serum creatinine to estimate GFR remains common place. The Schwartz formula (used in pediatrics) or the cockcroft-gault or modification of diet in renal disease formulas can be used to predict GFR coarsely. What was not pointed out by the authors is that most measures of GFR are done in chronic renal failure, in steady state, not acute renal failure where GFR is changing over a relatively short period of time as was the case in their study. This is primarily a matter of practicality. GFR is a moving target in the setting of acute renal failure and the most accurate measures of GFR require a steady state situation.

What is remarkable about this study is the degree of correlation between the iohexol clearance and creatinine based estimate. This probably relates to the uniformity of their study subjects (all female pigs weighing 25 kg-30 kg) and mechanism of injury. As a word of caution however, the formula derived to estimate GFR may not apply to chronic renal failure in their porcine model should the authors intend to study that disease process in the future. In the end, one could ask if measuring and comparing serum creatinine alone would suffice in this single renal unit model?

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