G
termination of glomerular filtration rate in anesthetized pigs by use of three-phase whole-kidney computed tomography and Patlak plot analysis

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Objective—To develop a whole-kidney computed tomography (CT) technique that would allow 3-point Patlak plot determination of glomerular filtration rate (GFR) and assess the correlation of GFR determined via CT (CT-GFR) with GFR determined via renal plasma clearance of inulin (Inu-GFR) in pigs.

Animals—6 healthy anesthetized pigs.

Procedures—Each pig underwent 3-phase whole-kidney helical CT (arterial, early, and late parenchymal phases) before and after contrast medium administration. After contrast medium administration, corrected Hounsfield unit values were determined for each kidney and the aorta. A 3-point Patlak plot for each kidney was generated, and plasma clearance per unit volume was multiplied by renal volume to obtain whole-animal CT-GFR. Correlations of mean Inu-GFR for the left and right kidneys (and combined [total] values) with the corresponding CT-GFRs were assessed via linear regression and Bland-Altman analyses.

Results—Left kidney, right kidney, and total CT-GFRs were good predictors of the respective Inu-GFR values ($r^2 = 92.3\%$, $r^2 = 85.5\%$, and $r^2 = 93.7\%$, respectively). For the left kidney, no significant bias between Inu-GFR and CT-GFR was detected. Right kidney and total CT-GFRs underestimated the corresponding Inu-GFRs (mean underestimation, $-8.4 \text{mL} \cdot \text{min}^{-1}$ and $-12.6 \text{mL} \cdot \text{min}^{-1}$, respectively).

Conclusions and Clinical Relevance—Three-phase whole-kidney CT with Patlak plot analysis of GFR may underestimate right kidney and total Inu-GFRs in pigs. The Patlak plot generated may be sensitive to nonlinearity caused by temporal variation in GFR. Nonetheless, the 3-phase CT approach offers some practical advantages for simultaneous evaluation of renal morphology and measurement of GFR. (Am J Vet Res 2008;69:1455–1462)

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CRI</td>
<td>Constant rate infusion</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>CT-GFR</td>
<td>Glomerular filtration rate determined via computed tomography</td>
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<tr>
<td>HU</td>
<td>Hounsfield unit</td>
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<tr>
<td>Inu-GFR</td>
<td>Glomerular filtration rate determined via renal plasma clearance of inulin</td>
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<tr>
<td>MAP</td>
<td>Mean arterial blood pressure</td>
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<tr>
<td>ROI</td>
<td>Region of interest</td>
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require readministration of contrast medium. Also, dynamic single-slice CT-GFR relies on the extrapolation of function from a single slice of parenchyma to the entire kidney, which has been speculated to be inaccurate when disease is nonhomogeneous. Multiphasic whole-kidney CT-GFR with subsequent 2- and 3-point Patlak plot determination to measure relative (split or percentage) and absolute renal function (ie, GFR) in humans has been described. Results of the 2-point Patlak method correlated highly with those derived via renal scintigraphy for the evaluation of relative and absolute renal function. Data obtained by use of the 3- (r = 0.84) and 2-point (r = 0.889) methods also correlated highly with GFRs determined via plasma clearance of iopromide in individuals with and without renal disorders.

The purpose of the study reported here was to develop a whole-kidney CT technique that would allow 3-point Patlak plot determination of CT-GFR and assess the correlation of CT-GFR with Inu-GFR in pigs. We hypothesized that CT-GFR values would correlate highly Inu-GFR values.

Materials and Methods

Animals—The study was designed according to the Canadian Council on Animal Care guidelines and approved by the institutional animal care and use committee. Six healthy young (3- to 4-month-old) male pigs (designated as pigs 1 through 6) were included in the study and used in random order. Each pig was premedicated IM with azaperone (2 mg•kg−1) and ketamine hydrochloride (15 mg•kg−1). After induction of anesthesia via IV administration (auricular vein) of fentanyl (0.005 mg•kg−1) and propofol (4 mg•kg−1), the trachea was orally intubated. Anesthesia was maintained via administration of isoflurane (1.5% to 2.5%) in oxygen and continuous infusion of lidocaine (3 mg•kg−1•h−1). Lactated Ringer’s solution was infused IV through a jugular catheter at a rate of 7 mL•kg−1•h−1 to meet maintenance needs during anesthesia for minimally invasive surgery. Electrocardiographic leads; a pulse oximeter; and probes for assessment of core (esophageal) temperature, anesthetic gas concentration, and inspired and expired CO2 concentrations were placed for monitoring purposes. Systemic arterial blood pressures and heart rate were monitored continuously by use of an indirect oscillometric technique. Rectal temperature was continuously monitored and maintained at approximately 38°C by use of a heating blanket.

Catheter placement—A 2-lumen polyurethane catheter was placed in the left external jugular vein of each pig for contrast medium administration and inulin CRI. A catheter was introduced into the common carotid artery for arterial blood sample collection and PCV measurement. Through a ventral midline laparotomy, both ureters were isolated and cannulated for urine collection. After instrumentation, an interval of 45 minutes was allowed to elapse to obtain a stable physiologic state prior to inulin administration.

Renal plasma clearance of inulin—Glomerular filtration rate was determined via renal plasma inulin clearance. An initial bolus of inulin was administered IV to each pig. The bolus consisted of 2.6 g of inulin dissolved in 10 mL of sterile water for injection and 10 mL of phosphate buffer solution; saline (0.9% NaCl) solution was added to a final volume of 50 mL, and pH was adjusted to 7.4 by use of an NaOH solution. Immediately after bolus administration, a CRI of inulin (1 mL•min−1) was delivered by use of a pump. To prepare the inulin solution for infusion, 0.5 g of inulin was dissolved in 2.5 mL of sterile water for injection and 6.0 mL of phosphate buffer; saline solution was added to a final volume of 125 mL, and pH was adjusted to 7.4 by use of an NaOH solution. The duration of the infusion was 100 minutes.

Once a steady state was reached (approx 30 minutes after the inulin CRI was started), the residual urine production of each kidney was collected for disposal (time 0 minutes [ie, T0 minutes]). Collection of blood and urine samples for determination of inulin concentration was begun. Starting at T3 minutes, arterial blood was collected at three 20-minute intervals (at T25, T45, and T65 minutes, respectively). Alternating with this and starting at T10 minutes, urine was collected in separate containers from the left and right kidneys at three 20-minute intervals (at T30, T50, and T70 minutes, respectively). Total urine flow was measured at each interval. Inulin concentration was measured in urine and plasma samples by use of an enzymatic assay. By use of a standard clearance formula, Inu-GFR was considered equal to renal clearance of plasma inulin (CLinu) as follows:

\[ \text{Inu-GFR} = \frac{\text{CL}_{\text{inu}}}{\text{C}_u} = \frac{\text{UF}}{\text{C}_u} \]

where UF is urine flow (mL•min−1), C is inulin urine concentration, and C is arterial plasma inulin concentration. Results of CLinu from T30 and T50 minutes were averaged for comparison with CT-GFR results.

CT image acquisition—By use of a single-slice helical scanner, CT-GFR was assessed a single time between T10 and T60 minutes. Baseline whole-kidney imaging was performed before contrast medium was administered. Three-phase whole-kidney imaging was performed during an arterial phase, an early parenchymal phase, and a late parenchymal phase following administration of contrast medium. Baseline whole imaging of both kidneys and the abdominal aorta was performed with a helical acquisition (5-mm slice thickness; pitch, 1; matrix, 512 × 512; display field-of-view, 30 cm; scan field-of-view, medium; 120 kVp; and 130 mAs). Subsequently, a pressure-injector was used to inject a bolus (0.25 mL•kg−1 [75 mg of iohexol] of iohexol (concentration, 300 mg•mL−1) at a rate of 4 mL•s−1. Computed tomographic acquisition (arterial phase) was initiated 4 seconds following the beginning of contrast medium injection. The entire kidney was scanned with the same settings as used during the baseline scan. Manual breath hold was used to arrest abdominal motion. A second scan (early parenchymal phase) was initiated 35 seconds after the beginning of injection, and a third (late parenchymal phase) was initiated 85 seconds after injection. Each scan was completed within approximately 20 seconds. Respiration was permitted between each scan.
Image analysis and CT-GFR calculation—The CT-GFR determination was based on Patlak plot analysis. On an image processing workstation, ROIs were manually drawn around the entire kidney on each image, excluding the renal hilus and main vessels. Measurements were repeated separately for the right and left kidneys. Edge detection software was not used because silhouetting between the renal contour and adjacent organs was occasionally present. Image window width and level were set at 150 and 20 HUs, respectively. Renal volume was calculated by adding the cross-sectional areas of each ROI for a given kidney and multiplying by slice thickness (5 mm). The mean HU value per kidney was calculated as follows: calculation of (mean slice HU value × slice ROI [mm²]) for all slices that included renal parenchyma, then multiplying by slice thickness (5 mm), and dividing by total kidney volume. The mean HU value of each kidney before contrast medium administration was subtracted from each value determined after contrast medium administration to provide a corrected kidney HU value (c[t]), which is related to the renal concentration of iodine.

An ROI of constant size (22 mm²) was centered in the abdominal aorta on each image obtained before and after contrast medium administration. The corrected aortic HU value was obtained by subtracting the ROI HU value obtained prior to contrast medium administration from each postadministration ROI HU value. Corrected aortic data within a given phase (arterial, early, and late parenchymal) were averaged to calculate b(t) for each phase, which is related to the whole-blood concentration of iodine. Aortic time-attenuation curves were generated for each phase (arterial, early, and late parenchymal), and the area under the curve was calculated for each phase. The area under the curve was divided by arterial blood iodine concentration ([Jb[t] dt/b(t)] at each phase, which is also known as normalized time.

A 3-point Patlak plot for each kidney was then generated by plotting b(t) dt/b(t) against c(t)/b(t) (Figure 1). The slope of each plot, which represented whole-blood iodine clearance, was corrected with the PCV value to obtain plasma clearance GFR (multiplied by 1 – PCV value). It is generally accepted that a Patlak plot in which the correlation (coefficient of determination, R²) between b(t) dt/b(t) and c(t)/b(t) is ≥ 0.95 is reliable.®

Iodine plasma clearance per unit volume for each kidney (mL·min⁻¹·mL tissue⁻¹) was then multiplied by renal volume to obtain global contrast medium clearance, or CT-GFR (mL·min⁻¹). Data are presented uncorrected for each pig’s body weight.

CT-GFR determined after oxytocin administration—As a pilot study, another identical CT-GFR scan protocol was repeated immediately following (within 30 seconds) administration of an IV bolus of 30,000 mg of oxytocin/kg in pigs 1, 2, and 3 at T60 minutes. Blood and urine samples for plasma inulin clearance determination were obtained immediately preceding and following the CT-GFR protocol (ie, within 5 [blood] and 10 [urine] minutes after oxytocin injection). A malfunction of the CT scanner occurred during acquisition on pig 2, and an adequate amount of data could not be acquired for analysis.

Statistical analysis—The mean and SD values of CT-GFR and Inu-GFR were obtained.α Because of the small sample size, Wilcoxon signed rank tests were used to compare the CT-GFR values for the left kidney with those for the right kidney, and the Inu-GFR values for the left kidney with those for the right kidney. Then, linear regression analysis was applied to compare CT-GFR with Inu-GFR for the left kidney, right kidney, and the summed values of both kidneys (total). The Inu-GFR (the gold standard) was designated as the independent variable, and CT-GFR was designated as the dependent variable. Bias was tested for by use of Bland-Altman evaluations. Because CT-GFR after administration of oxytocin was only performed on 2 pigs, only descriptive analysis was performed for those data. Significance was set at a value of P < 0.05 for all assessments.

Results

Weights of the 6 pigs used in the study ranged from 23 to 31 kg (mean weight, 26.7 kg). The PCV values ranged from 25% to 27% (mean PCV, 25.8%). Between T10 and T60 minutes, mean ± SD MAP and heart rate values for each pig ranged from 52.3 ± 3.2 mm Hg to

<table>
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<tr>
<th>Pig</th>
<th>Heart rate (beats/min)</th>
<th>MAP (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>93.6 ± 3.9</td>
<td>62.3 ± 2.0</td>
</tr>
<tr>
<td>2</td>
<td>94.5 ± 9.9</td>
<td>57.7 ± 7.1</td>
</tr>
<tr>
<td>3</td>
<td>107.0 ± 6.1</td>
<td>62.3 ± 3.2</td>
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<tr>
<td>4</td>
<td>96.1 ± 2.6</td>
<td>68.4 ± 2.0</td>
</tr>
<tr>
<td>5</td>
<td>95.7 ± 5.2</td>
<td>66.2 ± 3.4</td>
</tr>
<tr>
<td>6</td>
<td>97.0 ± 4.1</td>
<td>57.3 ± 4.4</td>
</tr>
</tbody>
</table>

Table 1—Mean ± SD heart rate and MAP for each of 6 anesthetized pigs during assessment of Inu-GFR and CT-GFR. After IV administration of a bolus of solution containing 2.6 g of inulin, an inulin CRI (1 mL·min⁻¹) was initiated; after 30 minutes, the residual urine production of each kidney was collected for disposal (time 0 minutes [ie, T0 minutes]). Assessments of Inu-GFR were made at T30 and T50 minutes, and assessment of CT-GFR was made once between T10 and T60 minutes. Blood and urine samples for plasma inulin clearance determination were obtained immediately preceding and following the CT-GFR protocol (ie, within 5 [blood] and 10 [urine] minutes after oxytocin injection). A malfunction of the CT scanner occurred during acquisition on pig 2, and an adequate amount of data could not be acquired for analysis.

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Table 2—Results of Inu-GFR (mL•min⁻¹) and CT-GFR (mL•min⁻¹) determinations for the left and right kidneys singly and in combination (total) in 6 anesthetized pigs.

<table>
<thead>
<tr>
<th>Kidney</th>
<th>Method</th>
<th>Pig</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Mean ± SD</th>
<th>Median</th>
</tr>
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<tbody>
<tr>
<td>Left</td>
<td>Inu-GFR</td>
<td></td>
<td>27.2</td>
<td>20.5</td>
<td>40.4</td>
<td>14.1</td>
<td>28.1</td>
<td>18.2</td>
<td>24.7 ± 3.8</td>
<td>23.7</td>
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<tr>
<td></td>
<td>CT-GFR</td>
<td></td>
<td>23.4</td>
<td>19.7</td>
<td>36.4</td>
<td>9.5</td>
<td>19.3</td>
<td>14.7</td>
<td>20.5 ± 3.6</td>
<td>19.5</td>
</tr>
<tr>
<td>Right</td>
<td>Inu-GFR</td>
<td></td>
<td>29.8</td>
<td>23.0</td>
<td>59.0</td>
<td>12.3</td>
<td>27.4</td>
<td>19.4</td>
<td>28.5 ± 6.6</td>
<td>25.2</td>
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<tr>
<td></td>
<td>CT-GFR</td>
<td></td>
<td>22.8</td>
<td>21.5</td>
<td>31.8</td>
<td>9.2</td>
<td>21.5</td>
<td>13.8</td>
<td>20.1 ± 3.2</td>
<td>21.5</td>
</tr>
<tr>
<td>Total</td>
<td>Inu-GFR</td>
<td></td>
<td>56.8</td>
<td>43.6</td>
<td>99.4</td>
<td>26.4</td>
<td>55.5</td>
<td>37.6</td>
<td>53.2 ± 10.3</td>
<td>49.6</td>
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<tr>
<td></td>
<td>CT-GFR</td>
<td></td>
<td>46.2</td>
<td>41.2</td>
<td>68.2</td>
<td>18.7</td>
<td>40.8</td>
<td>28.5</td>
<td>40.8 ± 6.9</td>
<td>41.0</td>
</tr>
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</table>

The CT-GFR and Inu-GFR results (without administration of oxytocin) were obtained for each pig; for each technique, the median, mean, and SD in each kidney were calculated for the group (Table 2). With regard to CT-GFR, there was no significant difference between the left and right kidney. Similarly, with regard to Inu-GFR, there was no significant difference between left and right kidney.

Results of linear regression analysis indicated a significant (P = 0.002) positive relationship between CT-GFR and Inu-GFR for the left kidney (Figure 2; Table 3). The slope was not significantly (P > 0.6) different from 1, and the y-axis was not significantly (P = 0.478) different from 0. For the left kidney, CT-GFR was a good predictor of Inu-GFR (R² = 92.3%).

Figure 2—Regression lines for CT-GFR (mL•min⁻¹) versus Inu-GFR (mL•min⁻¹) for the left kidney (A), right kidney (B), and kidneys in combination (total; C) in 6 anesthetized healthy juvenile pigs. In each panel, the straight line represents the linear relationship between CT-GFR and Inu-GFR.

For the right kidney, linear regression analysis revealed a significant (P = 0.008) positive relationship between CT-GFR and Inu-GFR (Figure 2; Table 3). The slope was significantly (P = 0.005) smaller than 1, but the y-axis was not significantly (P = 0.068) different from 0. As for the left kidney, CT-GFR was a good predictor of Inu-GFR in the right kidney (R² = 85.5%).

Linear regression analysis of the combined data from both kidneys revealed a significant (P = 0.002) positive relationship between CT-GFR and Inu-GFR (Figure 2; Table 3). The slope was significantly (P = 0.01) different from 1, but the y-axis was not significantly (P = 0.261) different from 0. The combination total CT-GFR was a good predictor of total Inu-GFR (R² = 93.7%).

For the left kidney, Bland-Altman analysis revealed no significant (P = 0.894) relationship (bias) between the difference between Inu-GFR and CT-GFR and the mean of those 2 measurements (Figure 3). However, for the right kidney and kidneys in combination, Bland-Altman analysis revealed a negative and significant relationship (right kidney, P = 0.014; combination total, P = 0.029); this indicated that as the CT-GFR and Inu-GFR values increased, the difference between them also increased, and that CT-GFR consistently underestimated Inu-GFR.

The mean difference between CT-GFR and Inu-GFR was –4.2 mL•min⁻¹ for the left kidney, –8.4 mL•min⁻¹ for the right kidney, and –12.6 mL•min⁻¹ for the kidneys combined. Ninety-five percent of the differences between these 2 techniques should be between –9.3 and –0.9 mL•min⁻¹ for the left kidney, between –26.9
and 10.1 mL•min\(^{-1}\) for the right kidney, and between −32.1 and 6.9 mL•min\(^{-1}\) for the combination total. Among the 6 pigs, pig 3 had CT-GFR and Inu-GFR values that were much higher than those for the remainder of the group; therefore, these values had a large influence on the linear regression analysis for the left kidney, right kidney, and combination total. Also, in the Bland-Altman analysis, the right kidney and total data for pig 3 were outlier values, which indicated a large difference between the difference in CT-GFR and Inu-GFR and the mean of these 2 values for this individual; this greatly influenced the outcome of the analysis. For this reason, linear regression analysis was repeated without inclusion of data from this individual (Table 3). On the basis of analysis of data from 5 pigs, the positive relationship between CT-GFR and Inu-GFR for the left kidney was not significant (\(P = 0.054\)). Compared with the previous findings, CT-GFR predicted Inu-GFR less well (\(R^2 = 76\%\)). For the right kidney, a significant \((P = 0.01)\) positive relationship between CT-GFR and Inu-GFR remained, and CT-GFR was a better predictor of In-GFR \((R^2 = 90.3\%)\). For the combination total, a significant \((P = 0.02)\) positive relationship between CT-GFR and Inu-GFR remained. However, CT-GFR predicted In-GFR less well \((R^2 = 87.8\%)\). Bland-Altman analysis was also repeated after data from pig 3 were removed. On the basis of this repeat analysis, there was no significant relationship (bias) between the difference between Inu-GFR and CT-GFR and the mean of these 2 measurements for the left kidney \((P = 0.75)\), right kidney \((P = 0.46)\), or combination total \((P = 0.38)\).

Following the administration of oxytocin in pigs 1 and 3, total Inu-GFR increased from 56.8 to 332.7 mL•min\(^{-1}\) and from 99.4 to 795.1 mL•min\(^{-1}\), respectively. There was no increase and even an apparent decrease in total CT-GFR (pig 1, 46.2 to 37.2 mL•min\(^{-1}\); pig 3, 68.2 to 57.9 mL•min\(^{-1}\)). Following oxytocin bolus administration, there was an increase in mean arterial pressure from 60 mm Hg to a maximum of 105 mm Hg at 2 minutes in pig 1 and an increase from 45 to 89 mm Hg at 3 minutes in pig 3. At 5 minutes, heart rate decreased from 97 to 89 beats/min in pig 1 and from 110 to 95 beats/min in pig 3.

**Discussion**

In the present study, a 3-phase whole-kidney CT-GFR technique similar to that previously reported\(^{13,15}\) was used. Use of single rapid bolus injections in the study pigs modified the timing of the arterial (10 seconds), early parenchymal (35 seconds), and late parenchymal (85 seconds) phases to more accurately reflect these phases. In pigs, peak aortic enhancement and renal enhancement occur at 4 to 8 seconds and 8 to 20 seconds, respectively.\(^{6}\) The early parenchymal phase replaced the short series of dynamic scans suggested by others to improve the aortic input function and added a third component to the Patlak plot.\(^{13,17}\) As in previous experiments,\(^{6,18}\) a low dose (0.25 mL•kg\(^{-1}\)) of contrast medium was used for this study.

Compared with single-slice dynamic CT-GFR determination, the 3-phase CT-GFR technique has 2 primary advantages. First, morphology of an entire kidney, including vasculature, can be evaluated at the time of maximal contrast medium enhancement. Second, data from the entire renal parenchyma are used to calculate renal function, thereby reducing possible errors from the extrapolation of information from a single CT slice.

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Table 3—Summary of results of linear regression analysis of the relationship between Inu-GFR and CT-GFR data for the left and right kidneys singly and in combination (total) in pigs; analysis was performed on data from 6 pigs and repeated on data from 5 pigs. *Slope and intercept values are presented as mean ± SE.

<table>
<thead>
<tr>
<th>Kidney</th>
<th>(R^2 (%))</th>
<th>Slope</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pigs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>92.3</td>
<td>0.94 ± 0.14</td>
<td>−2.79 ± 3.56</td>
</tr>
<tr>
<td>Right</td>
<td>85.5</td>
<td>0.45 ± 0.09</td>
<td>7.25 ± 2.96</td>
</tr>
<tr>
<td>Total</td>
<td>93.7</td>
<td>0.64 ± 0.08</td>
<td>6.32 ± 4.83</td>
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<tr>
<td>5 pigs*</td>
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<td></td>
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<tr>
<td>Left</td>
<td>76.0</td>
<td>0.79 ± 0.26</td>
<td>0.27 ± 5.70</td>
</tr>
<tr>
<td>Right</td>
<td>90.3</td>
<td>0.82 ± 0.15</td>
<td>−0.54 ± 3.58</td>
</tr>
<tr>
<td>Total</td>
<td>87.8</td>
<td>0.83 ± 0.18</td>
<td>−1.32 ± 6.09</td>
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*Outlier data obtained from pig 3 were removed.
The main disadvantage of the 3-phase CT-GFR technique is that renal time-attenuation curves cannot be made and aortic time-attenuation curves are incomplete. Additional useful information on iodinated contrast medium recirculation effects, renal transit dynamics, and the cause of renal dysfunction (ie, obstruction) provided by these curves is therefore not available.3-6

The Patlak plot should describe a linear relationship between \( c(t)/b(t) \) and \( \int \frac{db(t)}{b(t)} \), and a 95% correlation coefficient threshold is recommended to ensure that linearity is present. In the present study, the Patlak plot correlation was slightly less than this threshold for 3 kidneys (right and left kidneys in pig 3 and left kidney in pig 4), indicating a possible non-linear relationship between \( c(t)/b(t) \) and \( \int \frac{db(t)}{b(t)} \). This apparent nonlinearity has been explained physiologically by the fact that the early CT-GFR (between the arterial and early parenchymal phases) was higher than the later CT-GFR (between the early and late parenchymal phases).13 This temporal difference in GFR is thought to occur as a result of flow into and out of the interstitial tissue, a third compartment that is not accounted for with the Patlak plot model.15 This phenomenon illustrates a disadvantage of a plot with a small number of datum points: a single point can have a large influence on the correlation between sets of variables. However, data from 1 study15 that evaluated different 2-point Patlak plot combinations of a 3-phase CT-GFR acquisition suggested that only the arterial and late parenchymal phases were essential to ensure the highest correlation between CT-GFR and GFR determined via plasma clearance of iopromide. It is possible that we could have eliminated the early parenchymal data, thereby averaging the higher initial GFR and lower later GFR, and still have obtained good correlation of CT-GFR with Inu-GFR. Further evaluation is needed before recommending elimination of the early parenchymal data.

In the small group of healthy anesthetized pigs used in our study, GFR determined by use of the 3-phase whole-kidney CT technique and 3-point Patlak plot analysis correlated well with Inu-GFR when applied to the left kidney. In addition, CT-GFR did not significantly over- or underestimate Inu-GFR. These results differ from those of a previous study\(^a\) by our group in which the left kidney GFR determined via single-slice dynamic CT correlated poorly (\( R^2 = 47\% \)) with Inu-GFR. It is possible that because the entire renal parenchyma is accounted for in the renal attenuation calculation with the technique used in the present study, the minor temporal differences between contrast medium reaching the right and left kidneys become negligible. It is also possible that renal function in the left and right kidneys at the 3 sample times was more stable in the pigs of the present study.

When used to evaluate the right kidney and combination total GFRs, correlations of CT-GFR with Inu-GFR were high in the present study and equivalent (right kidney) or higher (total kidney) than correlations of GFR determined via the single-slice dynamic technique\(^a\) with Inu-GFR. However, there was significant underestimation of Inu-GFR by CT-GFR, whereas in our previous study\(^b\) no significant underestimation was identified. Several reasons could explain this bias.

First, only 6 pigs were used in the present study, and the influence of data from pig 3 on the analysis must be considered. Pig 3 had much higher CT-GFR and Inu-GFR values than the rest of the group; this did not seem to be related to changes in cardiovascular variables, although low MAP in this pig was associated with a compensatory high heart rate. It could be hypothesized that pig 3’s low MAP was attributable to a decrease in systemic vascular resistance, and the apparently maintained cardiac output resulted in higher GFR. Also, data from pig 3 were outlier values for the right kidney and combination total GFR values, because of the large difference between CT-GFR and Inu-GFR. When data from pig 3 were included in the analysis, the results for the right kidney were consequently skewed. This effect was evident when analysis was repeated without inclusion of pig 3’s data; as expected, the correlation between CT-GFR and Inu-GFR for the right kidney improved and the underestimation of Inu-GFR by CT-GFR disappeared. However, for the left kidney, values for pig 3 were not outliers, and the correlation between CT-GFR and Inu-GFR dramatically decreased likely because of the decrease in sample size caused by removal of this individual. It is also possible that the findings from pig 3 reflect a failure of the 3-phase whole-kidney CT-GFR technique to mimic Inu-GFR results at higher GFR values. Perhaps at higher values, the relationship between CT-GFR and Inu-GFR is nonlinear. Further studies on a group of individuals with high GFR (ie, during induced diuresis) would be necessary to evaluate this relationship.

Second, it is possible that CT-GFR truly underestimates actual GFR. It has been reported that CT-GFR underestimates the GFR calculated on the basis of inulin plasma clearance in pigs,\(^7\) that calculated on the basis of plasma iohexol clearance and nuclear scintigraphy in dogs,\(^7\) and that calculated on the basis of creatinine clearance in normal and abnormal kidneys in humans.\(^8\) Several causes have been suggested, including transient contrast-medium–induced nephrotoxicosis, underestimation of renal volume, vascular effects related to anesthesia, characteristics inherent to the type of contrast medium used, and the Fahraeus effect.\(^1,2,6,13\) Data collection at times later than the initial phase of glomerular filtration in the proximal tubule, as was performed in the present study, may also result in GFR underestimation via CT-GFR.\(^3\) Additionally, the fact that mean values of both medullary and cortical renal tissue are used in renal attenuation calculation likely also contributes to underestimation. Cortical tissue has a higher attenuation after contrast medium administration, particularly immediately following injection. During ROI placement, this higher cortical attenuation is averaged with lower-attenuation medullary tissue, thereby decreasing \( c(t) \) values and leading to lower CT-GFR values and underestimation of Inu-GFR. In the present study, it was not possible to differentiate cortical from medullary tissue, except during the renal enhancement peak. It has been suggested that Patlak plot analysis is more accurate when only cortical tissue is assessed.\(^3\) Regardless of the reason behind the underestimation of Inu-GFR by CT-GFR, the correlation between the 2 values was high,
and a correction factor could likely be determined and applied to CT-GFR values to correct for the underestimation.

No significant difference between the left kidney and right kidney GFRs was detected by use of the CT-GFR or Inu-GFR technique. This was expected for a group of healthy juvenile pigs and consistent with findings of our previous study.³⁵

One of the advantages of CT-GFR assessment relative to radionuclide evaluation of GFR is that CT-GFR assessment may be performed multiple times during a short period.³,⁶,⁹,10 This was evaluated as a pilot experiment in pigs 1, 2, and 3 following the administration of a high dose of oxytocin. It was unfortunate that data could not be collected for pig 2 and that the baseline right kidney and combined total CT-GFR results for pig 3 were outlier values, which further limited the results. In several species, including dogs and rats, high doses of oxytocin increase GFR through natriuretic and diuretic responses of the kidneys.²⁰–²³ However, these changes in GFR are not observed after administration of low doses of oxytocin.²¹ The natriuretic effect of oxytocin is mainly attributable to a reduction in tubular sodium reabsorption, probably in the terminal portion of the distal tubule or the collecting duct.²²,²⁶,²⁷ The mechanism of action of oxytocin involves stimulation of renal nitric oxide synthase in the proximal tubules and macula densa,²⁸ and the hormone possibly acts in concert with atrial natriuretic peptide to induce natriuresis via the common mediator cyclic guanosine monophosphate.²⁹ In the present study, CT-GFR did not change immediately following oxytocin administration, despite a marked increase in Inu-GFR. This failure of the CT technique to detect the marked oxytocin-induced increase in GFR is thought to be a result of inappropriate timing, rather than a measurement error; it is likely that there was not sufficient time between oxytocin administration and CT-GFR assessment for oxytocin to affect renal excretion. Determination of CT-GFR was initiated within 30 seconds of oxytocin administration; thus, GFR was measured at 30 to 140 seconds following oxytocin administration. In contrast, Inu-GFR was measured following CT, at 5 to 10 minutes after oxytocin injection; at those assessments, the observed increase in Inu-GFR was approximately 500% to 700%. A measurement error, caused by miscalculation of background renal and aortic values during a period when these values are highly variable (ie, during the first few minutes after injection), is unlikely. Determination of CT-GFR after oxytocin administration was performed several minutes following assessment of baseline GFR, and background renal and aortic density should have been stable by that time. In fact, scanning may be repeated after an interval as short as 15 minutes.³

An obvious limitation of CT-GFR determination in animals is the need for anesthesia, which may cause variation of GFR because of direct pharmacologic effects and the effects of anesthetic agents on cardiovascular variables. Presently, it is not possible to envision performing CT-GFR evaluation in awake animals, although with the use of faster multislice CT scanners, shorter durations of anesthesia will be possible. Further research is needed to compare the effects of various anesthetic drugs on CT-GFR, similar to experiments to determine optimal sedation protocols for radionuclide-based GFR determination in dogs.³⁶ Meanwhile, consistent use of a specific anesthetic protocol should minimize variation among individuals. Basic cardiovascular variables should also be closely monitored for changes that might explain abnormalities in GFR.

On the basis of results of the present study in pigs, GFR determination by use of 3-phase whole-kidney Patlak plot analysis correlates highly with GFR measured by use of renal clearance of plasma inulin but may consistently underestimate Inu-GFR. Studies in a larger number of animals and in those with high GFRs are necessary to confirm these findings and to establish a possible correction factor to compensate for the underestimation of Inu-GFR by CT-GFR. Because of the small number of datum points, the Patlak plot generated by this technique may be sensitive to nonlinearity caused by temporal variation in GFR. Despite these limitations, this 3-phase approach appears to offer some practical advantages for the evaluation of renal morphology simultaneous with measurement of GFR and may be considered as an alternative to single-slice dynamic CT-GFR determination.

References


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