Differential Renal Function in Unilateral Renal Injury: Possible Effects of Radiopharmaceutical Choice

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An abnormal filtration fraction or a significant divergence between a kidney's ability to extract Tc-99m dimercaptosuccinic acid (DMSA) and other function parameters, such as the glomerular filtration rate (GFR) or the effective renal plasma flow (ERPF), could lead to different estimates of relative or absolute renal function, depending on the radiopharmaceutical administered. To evaluate this possible divergence, we measured the relative GFR (I-125 iothalamate), ERPF (I-131 hippurate), and Tc-99m DMSA accumulation in adult male Sprague-Dawley rats with unilateral ureteral obstruction or unilateral ischemia at various times after renal injury. The relative ERPF of the obstructed kidney was significantly greater than the relative GFR at all time periods studied; significant but less dramatic differences were noted comparing DMSA with GFR in obstruction and DMSA and ERPF with GFR in ischemia. In evaluating renal disease, it is important to consider the functional parameter reflected by the administered radiopharmaceutical as well as the underlying disease state.

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Renal scintigrams are often obtained to determine differential renal function in patients undergoing evaluation for possible urologic surgery. The imaging is performed using one or a combination of different radiopharmaceuticals that reflect different parameters of renal function. The clearance of I-131 *o*-iodohippurate (OIH) is an indicator of the effective renal plasma flow (ERPF), and is essentially equivalent to the clearance of paraminohippurate (*1,2*). Technetium-99m DTPA indicates the glomerular filtration rate (GFR), having a clearance comparable with those of iothalamate and inulin (*3–5*). Technetium-99m dimercaptosuccinic acid (DMSA) binds to the cortical tubules and has been suggested to indicate functioning cortical mass (*6*). When these functional parameters decrease concordantly in a patient with renal disease, the measurement of differential renal function will be the same regardless of which radiopharmaceutical is used for the test. When these parameters do not decrease concordantly, the results will reflect both the underlying disease and the choice of radiopharmaceutical.

Recent reports have shown that there may be a significant divergence of functional parameters within a single kidney (*9–11*). This divergence appears more likely to occur in patients with renal ischemia, acute tubular necrosis, acute glomerulonephritis, congestive heart failure, or obstructive uropathy (*12–14*). A significant divergence in functional parameters could lead to different estimates of the severity of disease, or different estimates of differential renal function, depending on the radiopharmaceutical administered. To determine the degree to which different radiopharmaceuticals could give different measurements of relative renal function, we evaluated radiopharmaceuticals reflecting GFR, ERPF, and cortical mass in rats with unilaterally obstructed or ischemic kidneys.

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METHODS

Adult male Sprague-Dawley rats (400–500 g) were obtained commercially and kept under laboratory con-

ditions with free access to food and water. All procedures were carried out under general anesthesia induced by intraperitoneal sodium pentobarbital (50 mg/ml, 30 mg/kg body weight). Rats were divided into groups of five. Normal control animals were sham-operated. Experimental animals were subjected to permanent unilateral ureteral occlusion or transient unilateral renal-artery occlusion. For the former, one ureter was occluded by permanent double ligation using silk sutures, and studies were conducted at 6 hr or at 1, 3, 7, or 14 days after occlusion. In the second experimental model, the left renal artery was occluded for 30 min with a 1-in. bulldog clamp, and studies were conducted 6 hr, 24 hr, and 7 days.

At the time of assay, the rats with unilateral ureteral obstruction were again anesthetized with sodium pentobarbital as described above and the urethras were ligated. Ten-millicurie doses of I-131 hippurate, I-125 iothalamate, and Tc-99m DMSA were administered to each rat by a minicatheter inserted into a tail vein. Each dose was injected in a volume of 0.2 ml, and the catheter was flushed with 1 ml of saline (total of 1.6 ml). The syringes were counted before and after injection. Thirty minutes after injection, the animals were killed by cardiac puncture and exsanguination; the urinary tract was removed intact, and the samples were rinsed to remove residual blood. The unobstructed kidney, ureter, and bladder containing urine were counted in an automatic gamma well counter to determine excretion from the unobstructed kidney. The obstructed kidney, ureter, and urine proximal to the obstruction were counted to determine left-kidney excretion. Distinct photopeaks permitted I-131 and Tc-99m to be counted simultaneously; I-125 was counted after allowing time for Tc-99m decay. Estimates of relative renal function were based on the amount of radionuclide accumulated by each kidney and its corresponding collecting system.

The control animals and rats with unilateral ischemia underwent similar operations following pentobarbital anesthesia. The urethra was ligated, and the left ureter was ligated 2–3 cm distal to the renal pelvis. The measurements of relative renal function were performed as described above. All results were analyzed using paired t-tests.

RESULTS

Thirty minutes of distal ureteral obstruction under the conditions of the study had no measurable effect on the relative renal clearance of I-125 iothalamate, I-131 hippurate, or Tc-99m DMSA in the five control animals (Table 1). The 30-min renal uptake and excretion of I-131 hippurate was greater than that of I-125 iothalamate, which in turn was greater than that of Tc-99m DMSA. The results are to be expected, since hippurate reflects effective renal plasma flow (ERPF), iothalamate reflects glomerular filtration rate (GFR), and DMSA has a relatively low extraction efficiency (*7,8*).

There was a relative and absolute decrease in the renal function of the injured kidney following ureteral obstruction, as measured by all three agents, but the decrease was more pronounced for iothalamate than for hippurate or DMSA (Tables 1–3). The obstructed kidney showed a greater loss in the differential GFR compared with the differential ERPF at all time periods ($p < 0.01$); there was also a significantly greater loss in relative GFR compared with relative function measured with DMSA at 6 and 24 hr ($p < 0.01$). There was no significant difference in the relative function measured using hippurate and DMSA, except at 7 days after obstruction.

The relative GFR of the injured kidney at 6 hr after transient ischemia was significantly less than the relative ERPF or the relative function measured with DMSA ($p < 0.01$). There were no significant differences at other time periods. Although the 30-min period of obstruction used for data collection had no measurable effect on the normal kidneys, we cannot exclude the possibility that 30 min of obstruction may have had an effect on a kidney with preexisting ischemia, or that the results we obtained reflected both the preexisting ischemia and obstruction.

DISCUSSION

The rate of nephron filtration depends on four factors: (a) the rate of nephron plasma flow, (b) the systemic oncotic pressure, (c) the gradient of hydrostatic pressure between the glomerular capillary and Bowman's space, and (d) the glomerular hydraulic permeability coefficient (*13–17*). Since the nephron is an open space be-

TABLE 1
Percent of Total Renal Function Contributed by Injured Kidney following Obstruction or Ischemia*

	Hippurate	DMSA	Iothalamate
Control	51.6 ± 0.8	49.4 ± 0.7	48.2 ± 1.3
Obstruction			
6 hr	35.6 ± 1.8	36.4 ± 0.5‡	21.4 ± 0.6
1 day	25.6 ± 2.3†	25.6 ± 1.0‡	15.8 ± 1.8
3 days	18.8 ± 2.7†	13.6 ± 2.2	10.0 ± 2.0
7 days	22.8 ± 3.0†	14.0 ± 2.6§	12.0 ± 3.0
14 days	13.3 ± 2.2†	9.3 ± 1.0	6.3 ± 1.0
Ischemia			
6 hr	38.2 ± 3.1†	38.6 ± 3.1§	33.8 ± 3.6
1 day	17.8 ± 7.6	22.2 ± 6.3	16.2 ± 7.8
7 days	32.1 ± 5.4	30.0 ± 6.8	29.3 ± 6.7

* $\bar{x}$ ± s.e.m., five rats per data point.
† Hippurate compared with iothalamate, $p < 0.01$.
‡ DMSA compared with iothalamate, $p < 0.01$.
§ DMSA compared with hippurate, $p < 0.01$.

TABLE 2A
Percent of Injected Dose Cleared by Both Kidneys in 30 min*

	Hippuran	DMSA	Iothalamate
Control	73.4 ± 2.2	45.4 ± 2.5	65.2 ± 5.6
Obstruction			
6 hr	70.8 ± 1.3	42.1 ± 1.6	45.2 ± 1.6
1 day	65.6 ± 4.4	41.6 ± 1.2	49.4 ± 2.9
3 days	63.7 ± 1.7	41.8 ± 1.1	43.6 ± 2.3
7 days	68.3 ± 1.2	41.4 ± 1.1	58.2 ± 4.8
14 days	67.5 ± 1.9	36.5 ± 1.1	42.1 ± 0.3
Ischemia			
6 hr	67.1 ± 2.9	38.6 ± 4.3	49.0 ± 5.9
1 day	61.3 ± 2.1	36.8 ± 1.6	34.2 ± 3.6
7 days	64.1 ± 2.7	37.9 ± 1.4	39.8 ± 3.4

* $\bar{x}$ ± s.e.m., five rats per data point.

TABLE 2B
Percent of Injected Dose Cleared by Injured Kidney in 30 min*

	Hippuran	DMSA	Iothalamate
Control	37.9 ± 0.9	22.5 ± 1.2	31.4 ± 2.2
Obstructed			
6 hr	24.9 ± 1.6	15.3 ± 0.7	9.7 ± 0.5
1 day	17.1 ± 2.6	10.6 ± 0.4	7.8 ± 1.2
3 days	11.8 ± 1.6	5.8 ± 1.0	4.6 ± 0.9
7 days	15.7 ± 2.3	5.7 ± 1.1	7.6 ± 2.5
14 days	10.0 ± 1.5	3.8 ± 2.5	3.3 ± 0.5
Ischemic			
6 hr	25.8 ± 3.0	15.1 ± 2.5	17.0 ± 3.3
1 day	11.1 ± 5.1	8.4 ± 2.6	6.6 ± 3.5
7 days	21.2 ± 4.4	11.6 ± 2.9	12.6 ± 3.6

* $\bar{x}$ ± s.e.m., five rats per data point.

tween Bowman's space and the ureter, increases in ureteral pressure due to obstruction can be expected to result in a rise in pressure within the proximal tubule. Elevations in this pressure will decrease the hydrostatic pressure gradient, thus decreasing the rate of glomerular filtration. In theory, the intratubular pressure could rise high enough to reduce the glomerular filtration rate to zero without decreasing the effective renal plasma flow. In practice, the response to elevated ureteral pressure is affected by a number of other factors including a reduction in vascular resistance in the afferent arteriole (*18–20*), increased renal blood flow (*21,22*), a decrease in the hydraulic permeability of the glomerular capillary or of the glomerular capillary surface area (*13*), and eventually an increase in preglomerular arteriolar resistance (*23,24*).

In our studies, early unilateral ureteral obstruction clearly resulted in both an absolute and relative decrease in glomerular function as measured by I-125 iothalamate, this being more severe than the decrease in effective renal plasma flow measured by I-131 hippurate clearance. Similar but less striking results were also found between iothalamate and DMSA. By the 14th day of obstruction, there was severe functional deterioration measured by all three renal agents.

TABLE 3
Residual Functional Capacity of Injured Kidney (%)*

	Hippuran	DMSA	Iothalamate
Control	100	100	100
Obstructed			
6 hr	64.9	68.3	30.9
1 day	44.3	47.3	24.8
3 days	31.7	25.5	14.0
7 days	41.2	25.9	22.3
14 days	23.7	15.1	8.6
Ischemic			
6 hr	67.6	66.5	52.9
1 day	28.8	36.6	17.5
7 days	54.4	50.9	37.3

* $\bar{x}$ ± s.e.m., five rats per data point.

The relative function measured with Tc-99m DMSA paralleled the relative ERPF much more closely than the relative GFR. Other studies have also shown that the total plasma clearance of DMSA does not strictly follow changes in GFR (*26*). These results suggest that the renal uptake of DMSA may depend more on the tubular extraction of DMSA from the peritubular capillaries and interstitial space than reabsorption of filtered DMSA and from the tubular lumen. However, a recent study reports increased urinary excretion of DMSA in patients with tubular dysfunction; this is consistent with the hypothesis of tubular reabsorption of filtered DMSA (*27*). Additional studies will be needed to clearly determine the mechanism by which DMSA accumulates in the tubule.

In summary, the relative GFR suggests a much greater functional impairment of the damaged kidney in rats with unilateral ureteral obstruction or ischemia than do simultaneous measurements of relative function using DMSA or the ERPF. These results may be applicable to man and could lead to different estimates of absolute or relative renal function, depending on the radiopharmaceutical used. A technical error is not necessarily implied if two radiopharmaceuticals used to evaluate differential renal function give somewhat different results, which may reflect a change in the filtration fraction or different degrees of impairment in the handling of different radiopharmaceuticals by the damaged kidney. Note that the divergence of functional parameters may not be present, or so pronounced, in partial obstruction, and that in most clinical situations, measurements of relative renal function determined using these three agents tend to be concordant (*8,26,28,29*). Nevertheless, in evaluating patients with renal disease,

the functional parameter reflected by the choice of radiopharmaceutical must be considered as well as the underlying disease state, and in patients likely to have abnormal filtration fractions, it may be useful to use two radiopharmaceuticals to evaluate differential function, since the relative GFR and ERPF may be significantly different.

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