Quantitation of Renal Uptake of Technetium-99m DMSA Using SPECT

David Groshar, Alex Frankel, Galina Iosilevsky, Ora Israel, Boaz Moskovitz, Dan R. Levin, and Dov Front

Division of Nuclear Medicine, Rebecca Sieff Government Hospital, Safed; Departments of Nuclear Medicine and Urology, Rambam Medical Center and Technion-Israel Institute of Technology, Haifa, Israel

Quantitative single photon emission computed tomography (SPECT) methodology based on calibration with kidney phantoms has been applied for the assessment of renal uptake of [^{99m}Tc]DMSA in 25 normals; 16 patients with a single normal kidney; 30 patients with unilateral nephropathy; and 17 patients with bilateral nephropathy. An excellent correlation ($r = 0.99$, s.e.e. = 152) was found between SPECT measured concentration and actual concentration in kidney phantoms. Kidney uptake at 6 hr after injection in normals was 20.0% ± 4.6% for the left and 20.8% ± 4.4% for the right. Patients with unilateral nephropathy had a statistically significant ($p < 0.001$) low uptake in the diseased kidney (7.0% ± 4.7%), but the contralateral kidney uptake did not differ from the normal group (20.0% ± 7.0%). The method was especially useful in patients with bilateral nephropathy. Significantly ($p < 0.001$) decreased uptake was found in both kidneys (5.1% ± 3.4% for the left and 6.7% ± 4.2% for the right). The total kidney uptake (right and left) in this group showed to be inversely correlated ($r = -0.83$) with serum creatinine. The uptake of [^{99m}Tc]DMSA in single normal kidney was higher ($p < 0.001$) than in a normal kidney (34.7% ± 11.9%), however, it was lower than the total absolute uptake (RT + LT = 41.5% ± 8.8%) in the normal group. The results indicate that SPECT is a reliable and reproducible technique to quantitate absolute kidney uptake of [^{99m}Tc]DMSA.

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Several radionuclide methods have been suggested for evaluation of individual renal function (*1,2*). Technetium-99m dimercaptosuccinic acid ([^{99m}Tc]DMSA) has been recognized as the radiopharmaceutical of choice for static imaging and its uptake has been shown to correlate well with the effective renal plasma flow (ERPF), glomerular filtration rate (GFR) and creatinine clearance (*1,3,4*). Quantitation of renal uptake of [Tc] DMSA can be used as an index of the function of the cortical mass (*1*). Attempts at quantitation using planar scintigraphy have been reported (*3*), however, the need for correction for depth and background limits the repeatability and usefulness and prevented a widespread acceptance (*5*).

We have previously described and validated a quantitative SPECT method to measure in vivo volumes and concentration of radiopharmaceuticals in human tumors (*6–8*). In the present report the same method is used for measurement of individual kidney uptake of [^{99m}Tc]DMSA.

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For reprints contact: Dov Front, MD, PhD, Dept. of Nuclear Medicine, Rambam Medical Center, Haifa, 35254, Israel.

MATERIAL AND METHODS

SPECT Technique

The patient was injected intravenously with 2–4 mCi of [^{99m}Tc]DMSA and SPECT of the kidneys was performed 6 hr later. The SPECT method used for in vivo quantitation in human brain and lung tumors (*6,7*) was applied to the kidneys. The studies were performed using a rotating gamma camera (Elscint Apex 415-ECT, Haifa, Israel) and an all-purpose, low-energy collimator, and data was stored on an optical disk (Sudbury Systems Inc., Sudbury, MA). Data acquisition lasted 20 min and required 120 projection 3° apart using 64×64 byte mode matrix. The number of counts per projection was 2,500–4,000 and the entire study accumulated 3–5 × 10^5 counts. The raw data were reconstructed by the method of filtered backprojection using A Hanning filter. The filter is defined in the frequency domain as:

$$F(w) = 0.5\ w\ [1 + (\cos \pi w/n)] \qquad \pi = 3.14153,$$

where: w = frequency; n = Nyquist frequency.

After reconstruction, each image was sectioned at 1 pixel (0.68 cm) intervals along the transaxial, sagittal, and coronal planes. A computer program was written to calculate kidney volumes and radioactive concentrations based on the threshold value. A series of previous phantom studies (*6*) testing various threshold values showed that the best threshold was 43% of the maximal pixel activity. This threshold value is similar to the 46% value found by Tauxe et al. (*9*). The program first finds the maximal pixel activity in the slices selected by the operator as those which contain the whole extent of the kidney. The operator has to choose the best slice which will define the kidney and draw a region of interest (ROI) around the kidney. For volume measurements the number of pixels in all sections multiplied by the slice thickness (0.68 cm) is summed up. This results in a volume value expressed in voxels. The voxels are then converted to cc using the pixel to cc relation. For concentration measurements the threshold value is subtracted from all pixels in the ROI in all slices. All the nonzero pixels which have higher counts than the threshold value are used to calculate concentration. For each section the computer adds the number of the nonzero pixels within the region of interest. Counts per voxel are converted to concentration units (μCi/cc) using the regression line obtained previously by the comparison of phantoms with known concentration to the SPECT measurements of counts/voxel (*6*). The correlation coefficient of the comparison was 0.97 and the regression line was defined: counts/voxel = 1,492 μCi/cc − 88 (*6,7*).

Using this regression line and the number of counts/voxel provided by the program in each study, the concentration in μCi/cc can be calculated. The program asks for the amount of injected activity. The percent of injected dose per cc (%ID/cc) is calculated using this value corrected for radioactive decay. The kidney uptake was obtained by multiplying the kidney volume and %ID/cc.

Phantom Studies

A tissue equivalent water filled Alderson kidney phantom and shell simulating abdominal wall were used for the measurements. Phantom studies were performed using the same technique described above. Measurements were obtained with concentrations varying from 0.25 μCi/cc to 3 μCi/cc of ^{99m}Tc in both kidneys. One of the phantom kidneys contained 102 ml and the other 137 cc of water. Correlation between actual concentration (μCi/cc) and SPECT measured concentration (counts/voxel) was obtained.

Patient Studies

Technetium-99m DMSA SPECT study of the kidneys was performed on 88 patients 6 hr after the i.v. injection of 2–4 mCi of the radiopharmaceutical. The patients were divided in the following groups:

1. Normals. Twenty-five normal volunteers were investigated. They had no history of renal disease, normal laboratory values of serum creatinine and BUN and normal urinalysis. There were 17 males and eight females with a mean age of 34 (range 17 to 77).

2. Single normal kidney. Sixteen patients after nephrectomy and with a remnent normal kidney were included. There were six males and ten females with a mean age of 54 (range 32 to 77).

3. Unilateral renal disease. Thirty patients with unilateral renal disease were included. Twenty patients had hydronephrosis (as a result of uretero-pelvic junction stenosis, ureterolithiasis, nephrolithiasis, aberrant vessel, ureteral stenosis, tumor of ureter); three had hypernephroma; there were two pelvic kidneys, two hypoplastic kidneys, two pyelonephrites, and one renal artery stenosis. All had normal serum creatinine and BUN. There were 16 females and 14 males with a mean age of 44 yr (range 17 to 68 yr).

4. Bilateral renal disease. There were 17 patients with bilateral nephropathy, 11 males and six females, with a mean age of 51 yr (range 17 to 68 yr). There were 12 patients with hydronephrosis (as a result of bladder outflow obstruction, nephrolithiasis, ureterolithiasis, Ca of bladder) two polycystic kidneys; two bilateral pyelonephrites and one bilateral hypernephroma. The serum creatinine in this group ranged from 0.7 to 7 mg/dl.

Statistical Methods

Paired t-test was used to compare left versus right kidneys for the normal, bilateral, and unilateral groups. Unpaired Student's t-test was performed for comparison between groups. Sensitivity, specificity, and accuracy were calculated between normal kidneys (n = 50) with bilateral and unilateral diseased kidneys (n = 64).

RESULTS

Phantom Study

An excellent correlation (r = 0.99) was found between the SPECT measured concentration in the kidney phantoms and the actual concentration (Fig. 1).

Normals

In the normal subjects the volumes were 213 ± 34 cc and 209 ± 33 cc for the left and right kidneys, respectively. The %ID/cc was 0.099 ± 0.031 and 0.102 ± 0.028, the absolute kidney uptake was 20.0% ± 4.6% and 20.8% ± 4.4% for the left and right kidneys, respectively. The total absolute (right and left (rt + lt) kidneys) kidney uptake was 41.5 ± 8.8% (Table 1). There was no statistical significance difference between right and left kidney concerning the volume, %ID/cc and uptake.

Single Normal Kidneys

The volume was 275 ± 54 cc, the %ID/cc 0.13 ± 0.047 and the absolute kidney uptake 34.7 ± 11.9%. The absolute kidney uptake (Fig. 2) was significantly higher ($p < 0.001$) compared with kidneys of the normal group. This was the result of both the significantly greater volume of the kidneys ($p < 0.001$), and the increased %ID/cc ($p < 0.02$). However, uptake was significantly lower than the total (rt + lt) absolute uptake in normal kidneys ($p < 0.05$) (Table 1).

Unilateral Renal Disease

The normal kidney had a volume of 220 ± 43 cc; the %ID/cc was 0.09 ± 0.03 and the absolute kidney uptake 20 ± 7%. In the diseased kidney the volume was 128 ±

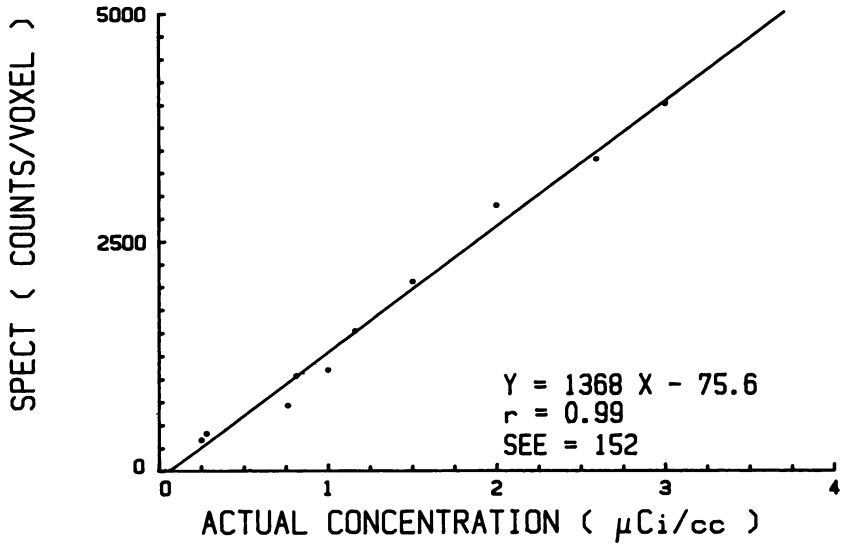

FIGURE 1
Correlation between SPECT measured concentration and actual concentration in kidney phantoms.

75 cc, the %ID/cc 0.05 ± 0.03 and the absolute kidney uptake was 7.0 ± 4.7%. The total absolute uptake (rt + lt) was 26.9 ± 8.3% (Table 1). The normal functioning kidney did not differ significantly from the normal group. The affected kidneys had a significantly ($p < 0.001$) reduced volume, %ID/cc and uptake compared with the contralateral normal kidney (Fig. 2). The total absolute uptake (rt + lt) in patients with unilateral kidney disease, however, was lower than in the normals ($p < 0.001$).

Bilateral Renal Disease

There was no statistical significant difference between both kidneys. The volume of the kidneys did not differ significantly from the normal group, however, there was a significantly ($p < 0.001$) reduced %ID/cc and uptake in the kidneys (Table 1) (Fig. 2). The total absolute uptake (rt + lt) in patients with bilateral disease was significantly reduced ($p < 0.001$) compared to the normals. The serum creatinine in this group inversely correlated ($r = -0.83$) with the total kidney uptake (rt + lt), (Fig. 3).

DISCUSSION

The assessment of the function of each kidney separately is important for diagnosis and follow-up of patients with renal disease. This is especially true in unilateral kidney disease, when normal laboratory values may be found in the blood even when more than half of the parenchyma is nonfunctioning (*5,10*). Split renal function studies require bilateral ureteral catheterization and is associated with discomfort and risks of trauma and infection (*10*). Technetium-99m DMSA has properties similar to mercurial diuretics and localizes in the proximal cortical tubules (*2*), and the kidney uptake of DMSA provides a practical index for the evaluation of cortical function. Quantitation of technetium-99m DMSA uptake has been attempted using planar scintigraphy (*3,4,11*). Variations in kidney depths and configuration and rotation and the need for accurate background subtraction are potential errors in absolute quantitation by planar scintigraphy.

Measurement of radiopharmaceutical uptake by SPECT has been achieved using a threshold method

TABLE 1
SPECT measured volume %ID/cc and Percent Uptake in Right and Left Kidneys

	Normal (= 25)		Single Kidney	Unilateral (N = 30)		Bilateral (N = 17)	
	Left	Right	(N = 16)	Diseased	Normal	Left	Right
Volume (cc)	213 ± 34 (146–282)	209 ± 33 (134–273)	275 ± 54 (200–364)	128 ± 76 (24–330)	220 ± 43 (106–317)	166 ± 83 (16–299)	202 ± 76 (96–420)
%ID/cc	0.099 ± 0.031 (0.050–0.02)	0.102 ± 0.028 (0.05–0.16)	0.130 ± 0.047 (0.068–0.24)	0.053 ± 0.031 (0.004–0.120)	0.090 ± 0.037 (0.04–0.18)	0.031 ± 0.020 (0.005–0.080)	0.036 ± 0.024 (0.005–0.087)
Uptake (%)	20.0 ± 4.6 (12.0–30.0)	20.8 ± 4.4 (12–31)	34.7 ± 11.9 (19.6–55.9)	7.0 ± 4.7 (0.4–16.5)	20.0 ± 7.0 (11.4–41.1)	5.1 ± 3.4 (0.3–10.5)	6.7 ± 4.2 (1.4–14.6)
Total Uptake (RL + LT)	41.2 ± 8.5 (25.6–61.2)		34.7 ± 11.9 (19.6–55.9)	26.9 ± 8.3 (15–49.4)		11.9 ± 5.8 (1.9–20.1)	

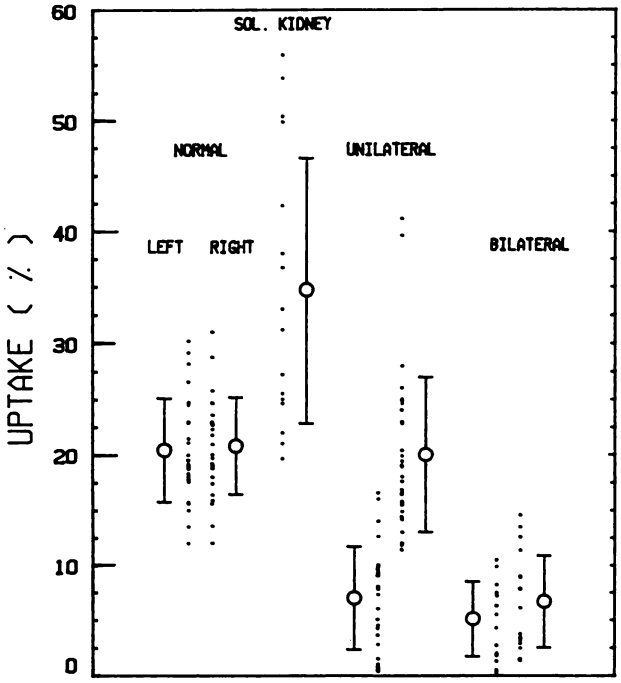

FIGURE 2
Kidney uptake in normals, single kidneys, patients with unilateral and bilateral renal disease with mean ±s.d..

(*6–8*). A threshold of 43% was found empirically to be highly reliable in a variety of phantoms and human tumors. The method does not deny that tissue attenuation is present but assumes that cancellation of attenuation effects occurs. Several factors can affect the quantitative reliability of SPECT: (a) the reconstruction algorithm with the chosen filter; (b) the angular and linear sampling; (c) the limited number of events; (d) the attenuation and the scattering of the gamma photons; (e) the algorithm used to define the target; and (f) the performance of the gamma camera. The reconstruction algorithm and filter are similar for all systems presently available. Factor 3 is inherent to nuclear medicine techniques. Consideration of the theoretic role of attenuation and the inability thus far to correct for it by the use of these theoretic methods has led us to use the threshold method and to demonstrate its usefulness and reliability by extensive phantom studies and ultimately by the only meaningful gold standard—the in vivo/in vitro correlation (*6*, *7*). An excellent correlation was found in this study when comparing the actual activity in the kidney phantom with that measured by SPECT, which indicates that the method can be reliably employed to measure concentration of [^{99m}Tc]DMSA in the kidneys. Also, the correlation found between total kidney uptake (rt+lt) and serum creatinine, in patients with bilateral disease is an indicator that the method can be used for evaluation of the function of the kidneys. Kawamura et al. (*3*) using planar techniques found the left kidney uptake to be 26.2 ± 6.5% and the right 27.8 ± 5.5% and the total kidney uptake 54 ± 8.8% 2 hr after injection. Arnold et al. (*12*), using a probe detector, studied only the left kidney avoiding background from the liver and found the uptake to be 20.3% 6 hr after injection. Our results are similar to their findings where the left kidney uptake was 20.0 ± 4.6% the right 20.8 ± 4.4% and the total kidney uptake 41.0 ± 8.5%. Renal uptake of DMSA may be affected by differences in preparations obtained by different manufacturers, also, the preparation is sensitive to oxidation which degrades the complex decreasing the uptake in the kidney. The timing of imaging and background subtraction problems may also be the cause of the differences in kidney uptake. Background subtraction probably constitutes a major problem in planar evaluation of DMSA uptake (*1*).

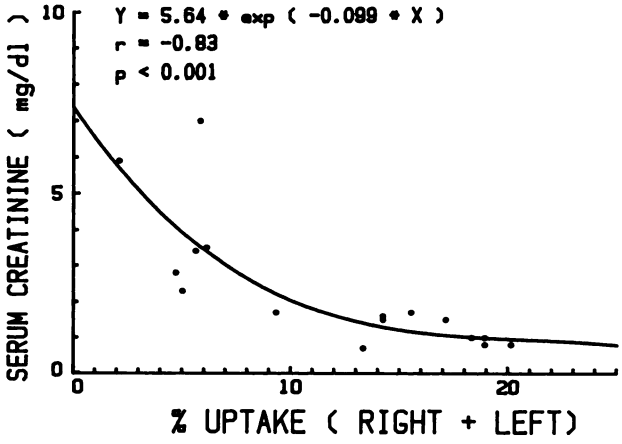

FIGURE 3
Correlation between total absolute kidney uptake (right+left kidneys) and serum creatinine in patients with bilateral renal disease.

There are several advantages in obtaining absolute quantitation rather than the more simple relative quantitation that merely determine the fractional distribution of function between the kidneys. In patients with a single normal kidney, we found the uptake to be higher than in each of the kidneys of normal controls. This is caused by an increased volume and concentration. The value of a normal single kidney was, however, lower than the total uptake of both kidneys in the normal group. The technique then gives a criterion for evaluation of a single kidney. Absolute quantitation may be also useful in the follow-up of patients with bilateral renal disease when the relative uptake may remain unchanged but the disease may progress or improve. Absolute quantitation also provides a normal/abnormal criterion for renal function. We found that with an uptake of 14.7% the sensitivity of the method was 95%, the specificity 92%, and an accuracy of 94% in separating normal kidneys from diseased kidneys.

In conclusion, SPECT appears to be a reliable technique to assess absolute individual kidney uptake of

[Tc]DMSA, which is useful in separating normal from disease kidneys. It could be used in nuclear medicine departments with a rotating gamma camera and computer facilities after defining the best suitable threshold for their equipment.

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