Technical note

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Influence of early (F + 0) intravenous furosemide injection on the split renal function using ^{99m}Tc-DTPA renography

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In busy nuclear medicine departments, the F + 0 protocol for diuretic renography is routinely used to shorten the acquisition time. The aim of this study was to evaluate the influence of the F + 0 protocol on the split renal function (SRF) during a dynamic renal scan using technetium-99m diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) compared with that using the standard technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA). A total of 102 patients referred for a dynamic renal scan for varied etiologies were divided into two groups: the F + 0 group, comprising 53 patients who were injected with furosemide just before ^{99m}Tc-DTPA injection, and the F + 10 group, comprising 49 patients who were injected with the diuretic at the 10th minute after radiotracer injection. All patients were also subjected to a static cortical ^{99m}Tc-DMSA scan with geometric quantification of SRF. A highly significant statistical difference ($P < 0.001$) was obtained on comparing the mean value of the difference in SRF calculated using DTPA and DMSA between the F + 0 and F + 10 groups, being 5.0±2.6 and 1.5±0.6%, respectively. All 49 patients in the F + 10 group had a difference in split function of 5% or less, whereas 17/53 patients representing 32.1% of the F + 0 group had a difference in SRF of greater than 5%. Early (F + 0) furosemide injection before administration of ^{99m}Tc-DTPA has a significant influence on the estimation of SRF of the diseased kidney (either obstructed or functionally impaired) when compared with furosemide injection after standard ^{99m}Tc-DMSA administration. Care should be taken during interpretation of the scan findings when accurate split function is required. *Nucl Med Commun* **34:354–358 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The use of radioisotopes in urinary system studies is dedicated to three major goals: quantification of renal function, dynamic imaging (renography), and parenchymal scintigraphy [1].

Diuretic renography is based on the premise that increased urine flow after furosemide administration causes rapid washout of the radiotracer from the unobstructed collecting system, but delayed radiotracer washout occurs if obstruction is present. However, furosemide is generally administered intravenously after filling of the pelvicalyceal system; its administration at the time of or before radiotracer injection also has been advocated. A number of factors may influence the diuretic renogram and must be taken into consideration for proper assessment. Timing of diuretic administration is not universally standardized in renography; the diuretic is administered 20 min after (F + 20), at the same time (F + 0), or sometimes 15 min before (F – 15) radionuclide injection [2].

Split renal function (SRF) is important in patients with unilateral renal disorders, pelvi-ureteric junction obstruction, or other obstructive uropathies. It is traditionally measured by radionuclide renal scintigraphy using different tracers, such as technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA), which is actively taken up by the proximal and distal renal tubular cells and accumulates in the renal cortex, and technetium-99m diethylene triamine pentaacetic acid (^{99m}Tc-DTPA), which is freely filterable at the glomerulus but neither secreted nor reabsorbed by the kidney tubules; it is used to measure total and individual kidney functions and the glomerular filtration rate (GFR) for each kidney [3].

Accordingly, the aim of the present study was to evaluate the effect of timing of intravenous injection of the diuretic (furosemide), whether at the same time of radiotracer injection (F + 0) or 10 min after radiotracer administration (F + 10), on the SRF measured using ^{99m}Tc-DTPA compared with that using standard ^{99m}Tc-DMSA.

Patients and methods

This prospective study was approved by the local ethics committee of our institution. The study included 102 patients with different renal disorders who were referred for both dynamic ^{99m}Tc-DTPA and static ^{99m}Tc-DMSA scans; patients who were not referred for the static DMSA scan were not included in the current study. The study included 33 female and 69 male patients.

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Their ages ranged from 2.5 months to 80 years, with a median value of 41 years. Patients with a single kidney, an ectopic (pelvic) or malrotated kidney, and severely impaired kidney function were excluded from the study. The patients were randomly distributed into two main groups: the F + 0 group, which included 53 patients who were administered furosemide just before ^{99m}Tc-DTPA injection at the zero time point as part of the routine protocol at our department, and the F + 10 group, which included 49 patients who were administered the diuretic at the 10th minute after radiotracer injection. Informed consent was obtained from patients in the latter group for modification of the technique.

A medical history was taken from each patient. Additionally, in all patients, blood urea and serum creatinine were estimated, and a radiological assessment by abdominopelvic ultrasonography and/or intravenous pylography was carried out if needed.

All patients in the present study underwent dynamic renal scintigraphy using ^{99m}Tc-DTPA and static cortical renal imaging using ^{99m}Tc-DMSA. Imaging was performed using a dual-head gamma camera equipped with an all-purpose, low-energy, parallel hole collimator covering an NaI(Tl) crystal of 3/8 inch thickness, set at 140 keV, with a 20% window, zoom 1.0 in adults and zoom 2.0 in children, using a matrix size of 64 × 64 for dynamic acquisition and 256 × 256 for static acquisition.

Patient preparation

An intravenous cannula was inserted into an antecubital vein and secured in all cases. Patients were instructed to be well hydrated by an oral intake of water at a level of 5–10 ml/kg over the 30–60 min preceding the dynamic study and to empty their urinary bladder just before entering the gamma camera room [4]. Breast feeding or feeding an external milk formula was encouraged for infants to keep them well hydrated and they were made to wear diapers to avoid urinary contamination. Sedatives were occasionally used in children to avoid movement during the dynamic study.

Diuretic renal imaging protocol

The preset Gates method [5], routinely used in our department for dynamic renal imaging with GFR and SRF calculation, was used in the current study. All patients lay in the supine position with the head of the camera placed posteriorly. Adult patients in the F + 0 group were intravenously injected with furosemide (0.5 mg/kg, with a maximum dose of 40 mg) just before being injected a bolus of 185 MBq (5 mCi) of ^{99m}Tc-DTPA, with adjustment of the dose of radioactivity for infants and children [6]. Acquisition of dynamic images started immediately with radiotracer injection at 1 s/frame for 1 min, followed by 15 s/frame for 80–120 frames. Alternatively, patients in the F + 10 group were administered the diuretic at the 10th minute after radiotracer injection, with continuation of serial dynamic imaging for 10–20 min more.

Regions of interest (ROIs) were drawn manually on a composite image (2–3 min after the injection) obtained by ^{99m}Tc-DTPA dynamic scintigraphy by a fixed-skilled nuclear medicine technologist. Time/activity curves (renograms) were generated and differential function of each kidney was calculated.

Static cortical renal imaging

All adult patients were intravenously injected with an average dose of 185 MBq (5 mCi) of ^{99m}Tc-DMSA, with adjustment of the dose in younger age groups. Static images were taken 2 h after tracer injection for a 500k count with a matrix size of 256 × 256 and zoom 1.0 in both anterior and posterior views. ROIs were marked over both kidneys in anterior and posterior views to quantify the renal split function as the geometric mean of counts in these ROIs according to the following equation:

$$\text{Split function of right kidney} = \frac{\sqrt{\text{Anterior} \times \text{posterior right kidney}}}{\sqrt{\text{Anterior} \times \text{posterior right kidney}} + \sqrt{\text{Anterior} \times \text{posterior left kidney}}} \times 100$$

Statistical methods

Data were statistically described in terms of mean and SD, median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was made using the Student *t*-test for independent samples. Within-group comparison of numerical variables was made using a paired *t*-test. For comparing categorical data, the χ^2-test was used. Fisher's exact test was used when the expected frequency was less than 5. Correlation between various variables was determined using Pearson's moment correlation equation. *P*-values less than 0.05 were considered statistically significant. All statistical calculations were performed using the computer program SPSS for Microsoft Windows (version 15; SPSS Inc., Chicago, Illinois, USA). In addition, Bland–Altman analysis was carried out to calculate the limits of agreement between the modalities.

Results

The F + 0 and F + 10 groups were almost matched for homogeneity in terms of age (mean = 36.1 ± 23.2 and 37.3 ± 25.6 years; median = 41 and 39 years, respectively), sex (16 and 17 male patients; 37 and 32 female patients, respectively), serum creatinine level, blood urea level, and total renal GFR. Corresponding values are displayed in Table 1.

The two patient groups were almost equivalent in terms of the mean and range of SRF of the diseased kidney, calculated using both ^{99m}Tc-DTPA and ^{99m}Tc-DMSA, as shown in Table 1.

Table 1 Distribution of the studied parameters between the F + 0 and F + 10 groups

	F + 0 group (N = 53)		F + 10 group (N = 49)	
Parameter	Mean±SD	Range	Mean±SD	Range
Serum creatinine (mg/dl)	1.6±1.3	0.3–6.0	1.9±1.8	0.2–9.0
Blood urea (mg/dl)	40.5±24.3	8–135	41.8±26.9	5–165
Total GFR (ml/min)	60.9±28.0	28–129	57.5±28.0	25–122
SRF of ^{99m}Tc-DTPA (%)	34.4±13.8	6–56	30.7±15.4	4–56
SRF of ^{99m}Tc-DMSA (%)	34.0±13.0	8–58	30.9±15.8	3–55

^{99m}Tc-DMSA, technetium-99m dimercaptosuccinic acid; ^{99m}Tc-DTPA, technetium-99m diethylene triamine pentaacetic acid; GFR, glomerular filtration rate; SRF, split renal function of the diseased kidney.

By analyzing the clinical indications and scintigraphic findings of the 102 patients referred to our department we found that they were referred for renal scintigraphy because of either obstructive (71 patients) or renal impairment (31 patients).

The mean difference in the percentage of SRF of the diseased kidney obtained using ^{99m}Tc-DTPA and ^{99m}Tc-DMSA was 5.0 ± 2.6% in the F + 0 group and 1.5 ± 0.6% in the F + 10 group, revealing a highly significant difference on statistical comparison between the two groups ($P < 0.001$).

We considered a cutoff value of 5% as a discrepancy between SRF obtained using ^{99m}Tc-DTPA and ^{99m}Tc-DMSA, which was significant for achieving the aim of our study. All 49 patients in the F + 10 group had a difference in SRF of 5% or less, whereas 17/53 patients representing 32.1% of the F + 0 group had a difference in SRF of more than 5%. A high statistically significant difference was obtained between the two groups ($P = 0.003$).

There was a trend toward overestimation (57/102 patients, 55.8%) of the SRF of the diseased kidney when measured using ^{99m}Tc-DTPA compared with that measured using ^{99m}Tc-DMSA; yet, a nonsignificant statistical difference was obtained between the groups ($P > 0.05$).

Pearson's test for numerical correlation revealed a nonsignificant correlation between the difference in SRF and all other studied parameters in both groups including the serum creatinine level, the blood urea level, and total renal GFR. Moreover, a nonsignificant correlation was also found between the difference in SRF and the estimated actual SRF of the diseased kidney obtained using ^{99m}Tc-DTPA and ^{99m}Tc-DMSA ($r = -0.9$ and -0.8 in the F + 0 group, $r = 0.2$ and -0.1 in the F + 10 group, respectively). Bland–Altman plots demonstrated a bigger difference in the mean SRF obtained using ^{99m}Tc-DMSA and ^{99m}Tc-DTPA in the F + 0 group compared with the F + 10 group, as shown in Fig. 1.

Discussion

Renal scintigraphies have been used for a long time to measure relative renal function. This procedure can be performed using different radiopharmaceuticals such as ^{99m}Tc-DMSA, ^{99m}Tc-DTPA, technetium-99m mercaptoacetyltriglycine, iodine-131 orthoiodohippurate [7], and, more recently, technetium-99m ethylene-L-L-dicysteine (^{99m}Tc-EC) [8].

Currently, in busy nuclear medicine departments such as ours, the F + 0 protocol is routinely used to shorten the acquisition time to only 20 min to allow the peak effect of the diuretic to take place in patients with suspected renal obstruction, especially in the pediatric age group [9,10], and to avoid the need for an additional venous puncture [11].

This practice was the rationale behind the present work that inquired into whether the simultaneous administration of furosemide with ^{99m}Tc-DTPA in dynamic renography (F + 0) might affect the calculation of SRF, aiming at standardization of the protocol for dynamic renal scintigraphy in our department.

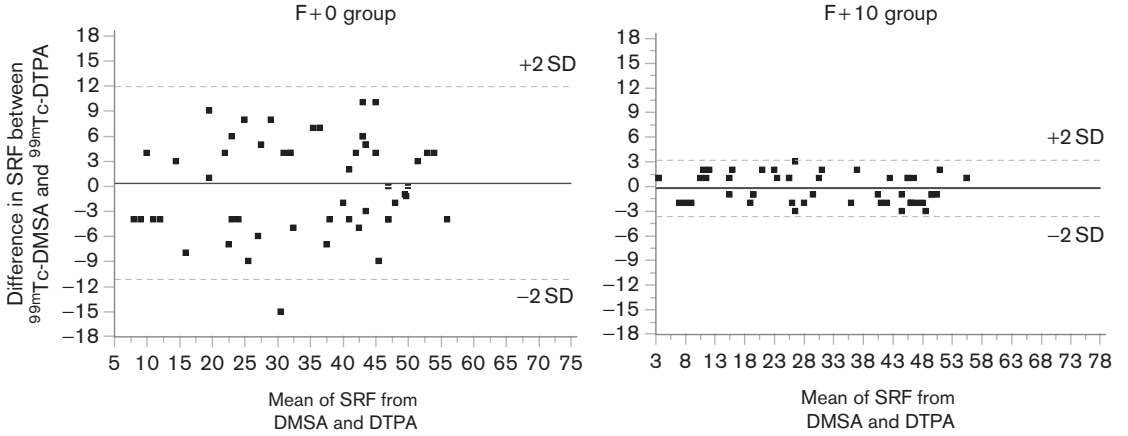
In this prospective, randomized study, we evaluated the influence of the timing of the diuretic injection on the SRF during dynamic renal scintigraphy using ^{99m}Tc-DTPA compared with that on the gold standard SRF calculated using ^{99m}Tc-DMSA.

Two groups of patients were studied: the F + 0 group, in which patients were routinely administered furosemide just before ^{99m}Tc-DTPA bolus injection, and the F + 10 group, in which patients were administered the diuretic at the 10th minute after radiopharmaceutical injection to eliminate the effect of the diuretic on the calculation of the SRF using the Gates method between 2 and 3 min, taking into consideration the fact that the diuretic usually takes effect within 1–2 min after intravenous administration, and its maximal effect occurs between 15 and 18 min [12,13].

The difference between SRF obtained using ^{99m}Tc-DMSA and that obtained using ^{99m}Tc-DTPA is mostly attributed to the discrete biological properties of radiopharmaceuticals, such as the mechanisms of renal excretion, as ^{99m}Tc-DTPA is excreted by glomerular filtration, whereas ^{99m}Tc-DMSA is excreted primarily by proximal convoluted tubules [8]. Other factors include renal cell retention, level of plasma-protein binding, and level of plasma clearance (^{99m}Tc-DTPA has a lower extraction efficiency of 20%) [14]. Moreover, the accuracy of the ^{99m}Tc-DMSA method can be attributed to the fact that it corrects for kidney depth by using the geometric mean individually, whereas the ^{99m}Tc-DTPA method accounts for only average differences in kidney depth in the Gates method and consequently is likely to underestimate background, which affects the split function [15].

The literature clearly mentions that SRF estimated using ^{99m}Tc-DTPA is not as accurate as that measured using

Fig. 1



Bland–Altman plots of the difference in SRF obtained using ^{99m}Tc-DTPA and ^{99m}Tc-DMSA versus the mean SRF obtained using ^{99m}Tc-DTPA and ^{99m}Tc-DMSA for the F+0 and F+10 groups. Solid line indicates the mean value of differences, and the dotted lines indicate the mean value of differences ±2 SD. ^{99m}Tc-DMSA, technetium-99m dimercaptosuccinic acid; ^{99m}Tc-DTPA, technetium-99m diethylene triamine pentaacetic acid; SRF, split renal function.

^{99m}Tc-DMSA, the gold standard [8]. In the current study, augmentation of this difference obtained using the two radiopharmaceuticals in the affected kidney was statistically elicited in the F + 0 group compared with the F + 10 group.

In our study the variation between SRF obtained using ^{99m}Tc-DTPA and that obtained using ^{99m}Tc-DMSA showed a statistically nonsignificant tendency toward overestimation with ^{99m}Tc-DTPA. This finding supports the assumption of Liu *et al.* [10], who stated that early use of a diuretic injection in a hydronephrotic kidney, whether or not obstructed, prompts washout of activity from its dilated renal collecting system, subsequently leading to overestimation of the renal function of this kidney. In contrast, early furosemide injection (F + 0) might result in an acceleration of renal transit and consequent underestimation of the renal function on the side with a short transit time (normal kidney) [16]. It is well known that the dominant hemodynamic effect of intravenous furosemide injection affects the renal blood flow. A recent study conducted by Wang *et al.* [17] confirmed this fact and concluded that intravenous furosemide injection significantly reduces both cortical and medullary renal blood perfusion in healthy kidneys using arterial spin labeling MRI. In addition, a short transit time results in an underestimation of the SRF if the calculation continues beyond the time when the activity starts to leave the kidney. This finding explains the subsequent reduction in SRF of the healthy kidney compared with the obstructed or hydronephrotic one. In the present study, although we tried to overcome this by applying an early short 2–3-min interval after tracer injection to calculate the SRF using the Gates method, the difference in SRF obtained using ^{99m}Tc-DTPA and ^{99m}Tc-DMSA between the F + 0 and F + 10 groups was statistically significant, assuming that this may be attributed to the definite effect of diuretic injection.

Approximately a third of the patients in the F + 0 group had an SRF difference of more than 5%, which could be attributed to the effect of furosemide in patients with a hugely dilated system or having substantially impaired renal function [8,18].

The discrepancy in split function between the F + 0 and F + 10 protocols will be of considerable value when accurate estimation of the SRF is essential – for example, in postoperative evaluation of obstructive uropathies or other disorders affecting one side of the kidney, such as unilateral ureteropelvic junction obstruction, before live donor nephrectomy, or in cases of impaired renal function [19,20].

Conclusion

Early (F + 0) furosemide injection simultaneously with ^{99m}Tc-DTPA administration during dynamic renal scintigraphy has a significant influence on the estimation of SRF of the diseased kidney when compared with furosemide injection with standard ^{99m}Tc-DMSA administration. Although the F + 0 diuresis protocol is less invasive and has a shorter imaging time, especially in busy nuclear medicine departments, caution should be exercised during interpretation of the scan findings when accurate spilt function is required. The technique of diuretic renography could be optimized according to the clinical indication and kidney function status.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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