# Quantitative Analysis of the Technetium-99m-DTPA Captopril Renogram: Contribution of Washout Parameters to the Diagnosis of Renal Artery Stenosis

Holley M. Dey, Paul B. Hoffer, Emanuel Lerner, I. George Zubal, John F. Setaro and Henry R. Black

*Section of Nuclear Medicine, Department of Diagnostic Radiology and Section of Cardiovascular Medicine, Department of Medicine, Yale University School of Medicine, New Haven, Connecticut; and Nuclear Medicine Service, Veterans Affairs Medical Center, West Haven, Connecticut*

Retrospective analysis of precaptopril and postcaptopril DTPA renograms from 88 hypertensive patients was performed to refine the quantitative criteria used to diagnose renal artery stenosis (RAS). Of the 88 patients, 45 had RAS and 43 had normal renal arteries at angiography. Using time-activity curves from the essential hypertensive group, diagnostic washout criteria for a positive DTPA renogram were developed. These were based on the 20 and 30 min/peak activity ratios in each kidney. When the washout criteria were retrospectively applied to patient data as a whole, sensitivity and specificity for RAS were 67% and 79%, respectively. When previously described uptake criteria, based on the time to peak activity in each kidney and the GFR ratio between the kidneys, were applied to the same data, sensitivity and specificity for RAS were 89% and 84%, respectively. Quantitative analysis of the DTPA renogram using the time to peak and GFR ratio was both sensitive and specific for RAS. Measurement of 20 and 30 min/peak renal activity ratios did not improve the accuracy of the test.

**J Nucl Med 1993; 34:1416–1419**

The sensitivity and specificity of captopril renography for diagnosis of renal artery stenosis (RAS) vary widely among published reports. In fact, sensitivities ranging from 70% to 100%, and specificities from 40% to 100% have been described (*1–5*). The reasons for these discrepant results are likely multiple, and relate to differences in experimental technique, radiopharmaceutical choice and diagnostic criteria applied to the data (*6*).

We have previously developed and reported quantitative diagnostic criteria for interpretation of the captopril-enhanced DTPA renogram (*1*). These criteria were based on the retrospective analysis of renograms from 23 clinically high-risk patients whose renal arteriograms were normal and who were presumed to have essential hypertension. Criteria for an abnormal DTPA scan included a time to peak (TTP) renal activity of ≥11 min on either the pre- or postcaptopril scan and/or a GFR ratio between the kidneys of >1.5 on the postcaptopril exam. Using these parameters, captopril renography provided 91% sensitivity and 87% specificity for RAS in a patient population with a high disease prevalence (n = 113) (*7*).

Despite our own encouraging results, others have reported more accurate detection of RAS with captopril renography. Sfakianakis et al. described 96% sensitivity and 95% specificity using diagnostic criteria based on the residual cortical activity of $^{131}$I-hippuran 20 min after tracer injection (*8,9*).

Our own experience with captopril renography has been based on the use of $^{99m}$Tc-DTPA. The advantages of the technetium-based tracer include on-site availability, cost and image quality. The technique is easy to perform and can be readily incorporated into clinical use at medical centers throughout the country. Our goal has been to maximize the quality of performance and analysis of the DTPA renogram for the detection of RAS.

In this study, we therefore decided to reanalyze our original data in order to compare the efficacy of DTPA washout parameters to quantitative uptake criteria (TTP-to-GFR ratio) in the detection of RAS. The aim of our study was to determine whether measurement of residual kidney activity would improve the sensitivity or specificity of DTPA captopril renography for RAS as compared to our original diagnostic interpretation.

## METHODS

Retrospective analysis was performed on pre- and postcaptopril DTPA renograms from 88 of the 113 patients that comprised the original study cohort. Computer files could not be retrieved for 8 of the remaining 25 patients and were of technically poor quality in 17 of the first cases performed. No significant differences between the included/excluded patients were identified. As has been

Received Dec. 14, 1992; revision accepted May 11, 1993.

For correspondence or reprints contact: Holley Dey, MD, Section of Nuclear Medicine, Dept. of Diagnostic Radiology, 333 Cedar St., Suite TE-2, New Haven, CT 06510.

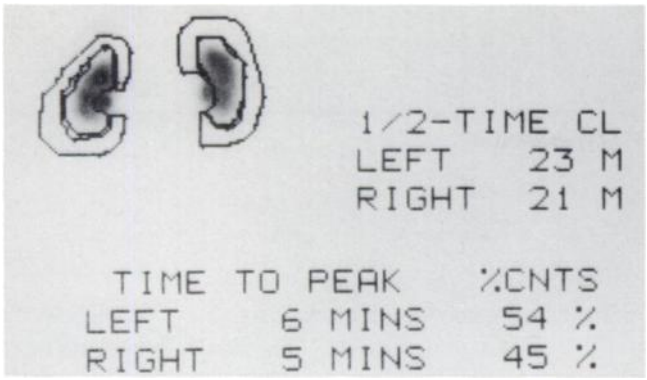


**FIGURE 1.** Manual ROIs were drawn around each kidney that excluded the renal pelvis. Background regions were drawn immediately adjacent to each kidney and used to correct for soft tissue contribution to counts within the renal ROI.

previously described (7), all patients were high-risk hypertensive with clinical signs and symptoms suspicious for RAS. Imaging was performed at baseline and after oral administration of 50 mg of captopril. Angiotensin-converting enzyme inhibitors were withheld for 24 hr prior to imaging; all other anti-hypertensive medications, including diuretics, were continued without interruption.

On the morning of the exam, patients were orally hydrated at home with at least 800 ml of water. A baseline renogram was then obtained after intravenous administration of 444 MBq (12 mCi) of $^{99m}$Tc-DTPA. Clinical experience at Yale-New Haven Hospital has shown that a 12-mCi tracer dose produces good analog images and reliable GFR measurements. Both analog and sequential 1-min digital images were subsequently acquired up to 35 min post-tracer injection. A 3-hr waiting period followed, during which time the patients were encouraged to continue oral hydration although the volume of fluid intake was not recorded. Captopril was then administered and renal scintigraphy repeated 1 hr later with a second 444-MBq dose of $^{99m}$Tc-DTPA. Data acquisition was begun 10 sec prior to isotope injection to allow subtraction of residual background activity from the computer images.

All patients enrolled in the study underwent digital subtraction arteriography with selective injection of the renal arteries within 6 wk of captopril renal scintigraphy (CRS). Criteria for a positive arteriographic result included renal arteries with greater than 75% stenosis or 50% stenoses with poststenotic dilatation. The results of angiography were available for comparison with CRS.

### Data Processing and Analysis

For the purpose of this study, digital image analysis was performed to generate quantitative uptake and washout parameters for each of 176 scans (pre- and postcaptopril scans for 88 patients). Regions of interest (ROIs) were manually drawn around each kidney that excluded the renal pelvis. Background ROIs approximately 6 pixels in diameter were drawn immediately adjacent to each kidney to allow correction of renal activity for soft tissue background (Fig. 1).

Renal time-activity curves were then generated for each background-subtracted ROI. From this curve, the following uptake and washout parameters were measured: TTP in each kidney, and the ratio of activity in each kidney at 20 and 30 min post-tracer injection to peak activity in that kidney. The GFR for both kidneys was estimated from activity within the renal ROI 3 min after injection using an in-house technique (*10*). The GFR ratio between the kidneys was calculated by dividing the larger GFR by the smaller result of the contralateral kidney. These measurements were repeated for each subject's pre- and postcaptopril scans. The TTP for both kidneys, the GFR ratio, and the 20- and 30-min-to-peak activity ratio for each kidney were recorded for all scans.

**TABLE 1**
Precaptopril and Postcaptopril Washout Parameter Values

| Parameter | Precaptopril (mean ± s.d.) | Postcaptopril (mean ± s.d.) |
|---|---|---|
| 20 min-to-peak ratio | | |
| Patent arteries | 0.54 ± 0.16 | 0.69 ± 0.27 |
| Stenosed arteries | 0.84 ± 0.43* | 1.00 ± 0.38* |
| 30 min-to-peak ratio | | |
| Patent arteries | 0.44 ± 0.16 | 0.60 ± 0.24 |
| Stenosed arteries | 0.69 ± 0.38* | 0.97 ± 0.47* |

*$p < 0.001$.

Of the 88 patients included in the study, 45 had RAS documented by angiography. Forty-three (49%) did not meet angiographic criteria for renal artery stenosis and were presumed to have essential hypertension. Normal ranges for the quantitative washout parameters, pre- and postcaptopril 20 min-to-peak and 30 min-to-peak activity ratios, were generated from the mean ± 2 s.d. of the results in the essential hypertensive group. Normal ranges for the quantitative uptake parameters, TTP and GFR ratio, were defined as TTP of <11 min and a GFR ratio of ≤1.5 based on previously described results (*1*).

Statistical analysis of the data was performed. Captopril induced changes in TTP, GFR ratio and 20 min-to-peak and 30 min-to-peak ratios were tested for significance using the two-tailed paired Student's t-test. Differences between RAS and essential hypertensive groups were evaluated using the unpaired t-test. The significance level for the t-tests was set at $p < 0.05$. Stepwise regression analysis was performed to determine the relative contribution of each of the quantitative parameters to the variance between the two groups (RAS versus essential hypertension).

The quantitative diagnostic criteria were then retrospectively applied to the patient data and each study classified as either RAS or NO RAS based on whether the normal range for either/both the uptake and washout parameters had been exceeded. The sensitivity and specificity of both the uptake and washout criteria for RAS in this hypertensive population were calculated with angiography as the measured gold standard.

## RESULTS

Residual kidney activity was measured at 20 and at 30 min post-DTPA injection and the result expressed as a fraction of peak counts in the region. Twenty and thirty minute-to-peak ratios were calculated for all subjects and compared between two study groups: arteries meeting angiographic criteria for RAS and arteries that did not meet those criteria. The mean 20 min-to-peak ratio for patent arteries was 0.54 pre-captopril and 0.69 after captopril administration. At 30 min, the mean activity ratio was 0.44 pre- and 0.60 postcaptopril. The standard deviation of these measurements was high, and greater on the postcaptopril than on the pre-captopril scan (Table 1). For all

**TABLE 2**
Positive $^{99m}$Tc-DTPA Captopril Renogram

| | |
|---|---|
| Precaptopril | |
| 20 min-to-peak ratio | ≥0.87 |
| 30 min-to-peak ratio | ≥0.77 |
| Postcaptopril | |
| 20 min-to-peak ratio | ≥1.23 |
| 30 min-to-peak ratio | ≥1.09 |

**TABLE 4**
Stepwise Regression Analysis

| | Model r |
|---|---|
| GFR ratio | 0.74 |
| TTP | 0.77 |
| 30 min-to-peak ratio | 0.78 |
| 20 min-to-peak ratio | 0.78 |

combinations of 20 and 30 min-to-peak ratios, and pre- and postcaptopril conditions, the difference between the means of the normal and stenosed artery groups was statistically significant at the $p < 0.001$ level. The difference between the pre- and postcaptopril values within each group was also significant, consistent with a captopril-induced effect on renal washout. Nonetheless, considerable overlap in parameter value range between the patent and stenosed artery groups was evident.

From these results, new quantitative criteria were created for a positive DTPA captopril renogram. These were based on 20 and 30-min-to-peak ratios two standard deviations above the mean values observed in kidneys supplied by patent arteries. These criteria are presented in Table 2.

The quantitative washout criteria were then retrospectively applied to the patient data, and a 20 or 30-min-to-peak ratio on either the pre- or postcaptopril scan exceeding the established normal range considered a positive result. Using these criteria, 30 of 45 kidneys with RAS were true positive and 34 of 43 kidneys without RAS were true negative for an overall sensitivity of 67% and a specificity of 79% (Table 3). The positive predictive value of the test was 0.77, the negative predictive value 0.69.

When the original diagnostic criteria, based on TTP and the GFR ratio, were applied to this same set of 88 patients, 40 of 45 studies were true positive and 36 of 43 studies were true negative for a sensitivity of 89% and a specificity of 84% (Table 3). The positive predictive value of the test was 0.85, the negative predictive value 0.88.

Sensitivity and specificity were unchanged, at 89% and 84% respectively, when washout and uptake criteria were used in combination. The addition of quantitative washout parameters to the diagnostic standard did not increase the accuracy of the test.

Stepwise regression analysis was then performed to determine the relative contribution of each of the quantitative parameters to the variance between the two groups of patients (with and without RAS). As shown in Table 4, the GFR ratio best explained the statistical difference between the NO RAS and RAS studies, while the TTP made a small contribution to the variance, and the effect of the 20- and 30-min-to-peak ratios was negligible.

**TABLE 3**
Sensitivity, Specificity and Predictive Values

| Diagnostic criterion | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|---|
| Original* | 0.89 | 0.84 | 0.85 | 0.88 |
| Washout† | 0.67 | 0.79 | 0.77 | 0.69 |

*Original diagnostic criteria = TTP and GFR ratio.
†Washout criteria = 20 and 30 min/peak ratios.

## DISCUSSION

The successful detection of RAS with captopril renography is influenced by technical aspects of the test. The choice of radiopharmaceutical and imaging protocol both impact on study outcome. Several investigators, for example, have found that $^{123}$I and $^{131}$I-orthoiodohippurate are more sensitive to captopril-induced changes in renal function than $^{99m}$Tc-DTPA in patients with renal failure (*11–13*).

The accuracy of CRS is also affected by the method of diagnostic interpretation of renal images and time-activity curves. We previously described quantitative diagnostic criteria for the analysis of the DTPA captopril renogram based on the TTP uptake in each kidney, and the GFR ratio between the kidneys (*1*). These criteria were found to provide the greatest sensitivity (91%) and specificity (87%) for RAS when parameters including kidney GFR, total GFR, GFR ratio and TTP were compared. Scintigraphic measurement of kidney GFR was found to be a relatively insensitive predictor of RAS for at least two reasons. First, kidneys affected by unilateral RAS and poor pre-captopril renal function showed a variable response to captopril administration and could not be identified on the basis of GFR change. Second, the kidney GFR of essential hypertensive patients showed considerable overlap with the kidney GFR of patients with renal artery stenosis.

The purpose of the current study was to determine whether quantitative washout parameters derived from the $^{99m}$Tc-DTPA renogram could improve the sensitivity and/or specificity of CRS for RAS as compared to those parameters (GFR ratio and TTP) which in our experience have been most successful in detecting disease.

We found that while the mean washout parameters, defined as the 20- and 30-min-to-peak activity ratios, were significantly different between the patent and stenosed renal artery groups, the standard deviation around the means was large, leading to overlap between the groups. This overlap precluded the accurate identification of subjects with RAS. Compared to quantitative uptake criteria, DTPA washout criteria were less sensitive and specific for the detection of RAS. No additional true-positive cases of

RAS were identified using washout criteria beyond those detected with TTP and GFR ratio standards.

We have previously reported that therapy with angiotensin converting enzyme inhibitors (ACEI) may decrease the sensitivity of DTPA captopril renography. In order to determine whether the poor sensitivity of washout parameters for RAS could be attributed to the use of ACEI, we compared the sensitivity of 20 and 30-min-to-peak ratios in the 28% of patients on chronic ACEI therapy against the 72% who were not. Sensitivity was equally poor (66% and 67%, respectively).

We also found that for kidneys both with and without RAS, the mean renal washout ratios were greater after captopril administration. Mean renal transit time was slowed by 28% over baseline. This finding is consistent with a captopril-induced delay in renal transit and was anticipated in the presence of RAS but not in its absence. Others have reported that mean washout of $^{131}$I-hippuran from cortical ROIs is unchanged by captopril administration in the absence of RAS (*8*). The fact that cortical transit of $^{99m}$Tc-DTPA was slowed by captopril may suggest an intrinsic difference in the renal processing of hippuran versus DTPA. Alternatively, slow washout of DTPA could have been due in part or in combination to poor hydration, prominent calyceal activity or concurrent renal failure. Our subjects were orally hydrated prior to the pre-captopril scan with a known volume of water and encouraged to replace fluid losses between the pre- and postcaptopril scans. However, the amount of fluid ingested between scans was not standardized and was not recorded at the time this study was performed. It is therefore possible that some patients were not fully hydrated at the time of the postcaptopril exam, leading to delayed washout (*11*).

Calyceal activity could not be entirely excluded from the manually drawn cortical ROIs. Retention of activity within the collecting system could therefore have contributed to the apparent slow renal washout of DTPA. Finally, the mean serum creatinine for our patients was 1.7 mg/dl with a range of 0.6–11.0, consistent with mild to marked renal failure in approximately half of the study population. The DTPA clearance rate from renal cortex would have been decreased in these patients.

Interestingly, Fine et al. have also reported delayed renal transit after captopril administration to patients with essential hypertension (*14*). The authors attributed this finding to retention of activity within the renal pelvis, and noted that cortical ROIs showed enhanced washout.

We conclude that quantitative analysis of the $^{99m}$Tc DTPA captopril renogram using the TTP and GFR ratio is both sensitive and specific for RAS in a high-risk, hypertensive population. We recommend the use of these standards during routine diagnostic interpretation of captopril renography and feel that the results can be effectively used to select patients for renal arteriography. Our experience suggests that measurement of 20- and 30-min-to-peak renal cortical activity ratios does not improve the accuracy of the test for RAS and we do not recommend the addition of these criteria to the standard diagnostic algorithm.

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