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Value of the Filtration Fraction Assessed by Dynamic ^{99m}Tc-Diethylenetriaminepentaacetic Acid Renal Scintigraphy After Angiotensin-Converting Enzyme Inhibition for the Diagnosis of Renovascular Hypertension

Eonwoo Shin[1] · Changhwan Sung[1] · Hye Joo Son[1] · Dong Yun Lee[1] · Sun Young Chae[1] · Dae Hyuk Moon[1]

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Abstract

Purpose This study aimed to determine the diagnostic value of the relative filtration fraction (RFF) assessed by dynamic ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) renal scintigraphy after angiotensin-converting enzyme (ACE) inhibition for renovascular hypertension (RVHT) diagnosis.

Methods ^{99m}Tc-DTPA captopril renal scintigraphy performed in adolescents or adults (≥ 10 years) with suspected RVHT was retrospectively reviewed. The RFF of the affected kidney was qualitatively assessed as the relative glomerular filtration rate during the 2 to 3-min period compared with the relative perfusion during the first 60 s (qualitative RFF) and scored from 1 (definitely same) to 5 (definitely decreased). The quantitative RFF of the affected kidney was obtained by dividing the percentage of glomerular filtration rate by the percentage of renal perfusion.

Results Overall, 173 patients (high probability, $n = 15$; and low probability, $n = 158$) were included based on conventional captopril renal scintigraphic criteria. An abnormal qualitative RFF was observed in 12 patients with high probability, and the diagnostic sensitivity was 80.0% (95% CI, 51.9–95.7). The RFF was normal in 152 patients with low probability, and the diagnostic specificity was 96.2% (95% CI, 91.9–98.6). The RFF was lower in patients with high probability than in those with low probability (0.79 ± 0.15 vs. 1.02 ± 0.11, $P < 0.0001$).

Conclusions The RFF assessed by dynamic ^{99m}Tc-DTPA renal scintigraphy after ACE inhibition can detect patients with high probability for RVHT. The RFF after ACE inhibition might be a useful diagnostic criterion especially when baseline scintigraphy is not available for evaluating ACE inhibition-induced changes.

Keywords ^{99m}Tc-diethylenetriaminepentaacetic acid renal scintigraphy · Angiotensin-converting enzyme inhibition · Renovascular hypertension · Filtration fraction

Introduction

Renovascular hypertension (RVHT) is defined as systemic hypertension resulting from a compromised renal artery, often due to main artery stenosis [1]. RVHT is one of the most common causes of secondary hypertension [2] and one of the few correctable causes of hypertension. However, the cause-and-effect relationship between renal artery stenosis and hypertension is complex, and indiscriminate revascularization is no longer justified [3–6]. Renal scintigraphy after angiotensin-converting enzyme (ACE) inhibition can detect functionally significant renal artery stenosis and thereby predict the response to revascularization [7–10]. ACE inhibitors block the conversion of angiotensin I to angiotensin II, inhibiting kininase II [11, 12]. Consequently, in patients with RVHT, angiotensin-enzyme inhibitors cause efferent arteriolar dilation and thereby lower the transcapillary pressure that maintains glomerular filtration [13]. The resulting decrease in glomerular filtration is manifested as a decrease in renal uptake or renographic changes [14]. The probability for RVHT is high when there is a marked change in the renogram

✉ Dae Hyuk Moon
dhmoon@amc.seoul.kr

[1] Department of Nuclear Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympicro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea

curve after ACE inhibition compared with baseline findings [15], which is based on two separate renal scintigraphic studies before and after ACE inhibition.

Unlike the glomerular filtration rate, the renal blood flow of the stenotic kidney before and after ACE inhibition is not greatly different; thus, it is difficult to discriminate patients with essential hypertension and patients with RVHT [14, 16]. Indeed, ACE inhibition-induced changes in renal plasma flow markers in the stenotic kidney are largely dependent on a decrease in the glomerular filtration rate [14]. Therefore, the filtration fraction (the ratio of the glomerular filtration rate to the renal plasma flow rate) is expected to decrease in patients with RVHT. If a flow study is conducted for the first 60 s during renal scintigraphy after ACE inhibition, the filtration fraction can be assessed, and it might serve a complementary role to enhance the accuracy of the study in selected cases [13].

The objective of this study was to investigate the diagnostic value of the relative filtration fraction (RFF) assessed qualitatively and quantitatively by dynamic ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) renal scintigraphy (hereinafter referred to as qualitative and quantitative RFF, respectively) after ACE inhibition for the diagnosis of RVHT in our retrospective cohort. The quantitative assessment of renal perfusion is not standardized and can be affected by methodological errors or variations associated with radiotracer injection and quantitative methods [17, 18]. Nevertheless, the relative perfusion as a ratio of the subject kidney to the contralateral normal kidney may be more reliable [19], and the methodology would be similar to the assessment of the relative glomerular filtration rate. The ratio of the relative renal perfusion to the relative glomerular filtration may not be affected by methodological sources of variability. Therefore, we included patients with unilateral parenchymal retention or changes in the relative renal function after ACE inhibition and excluded patients with bilateral symmetrical cortical retention or decreased uptake of ^{99m}Tc-DTPA.

Materials and Methods

Study Design and Patients

We retrospectively reviewed our hospital database of adolescents or adults (≥ 10 years) who underwent ^{99m}Tc-DTPA captopril renal scintigraphy with a clinical suspicion of RVHT from March 2007 to December 2017. Patients with high or low probability for RVHT on ^{99m}Tc-DTPA captopril renal scintigraphy were included [15]. If there was no baseline ^{99m}Tc-DTPA renal scintigraphy despite abnormal captopril renal scintigraphy, patients with marked unilateral delayed excretion accompanied by a reduction in the relative uptake (greater than 20% compared with the contralateral kidney) were regarded as having a high probability as per guideline recommendation [13, 15, 20]. We excluded patients whose captopril renal scintigraphy showed a single functional kidney or indicated intermediate probability [15, 21]. If a baseline study was not performed, patients with a small, poorly functioning kidney without prolongation of the renal transit time on captopril renal scintigraphy were regarded as having an intermediate probability [13, 21]. This study was approved by the Asan Medical Center Institutional Review Board for Human Research. Written informed consent was waived.

^{99m}Tc-DTPA Captopril Renal Scintigraphy

^{99m}Tc-DTPA captopril renal scintigraphy was conducted following a standardized 2-day protocol [15]. Patients were asked to withhold ACE inhibitors and angiotensin II receptor blockers for 3–7 days depending on the half-life before captopril renal scintigraphy. A single dose (25 mg or 1 mg/kg for adolescents aged 15 or younger) of captopril was given orally 60 min before the administration of ^{99m}Tc-DTPA. The patients were asked to drink 500–1000 mL (7 mL/kg for adolescents aged 15 or younger) of water 30–60 min before the study. After injecting an intravenous bolus of 370 MBq (8.7 MBq/kg for adolescents aged 15 or younger) of ^{99m}Tc DTPA, the patients were positioned supine under a conventional gamma camera equipped with a low-energy all-purpose collimator. Dynamic images were acquired for a total of 20 min (every 1 s for 1 min and every 30 s for the following 19 min). To generate time-activity curves for further analysis, regions of interest (ROIs) were drawn over each kidney and the background at the lower-outer perirenal region. If the ^{99m}Tc-DTPA captopril renal scintigraphy was normal, baseline renal scintigraphy was not performed. The renal uptake of ^{99m}Tc-DTPA was measured for each kidney during the 2–3 min period. ^{99m}Tc-DTPA captopril renal scintigraphy was used to determine whether the patients had high, low, or intermediate probability for RVHT by board-certified nuclear medicine physicians [15, 20]. Patients with high probability for RVHT were regarded as having RVHT for the purpose of this study.

Analysis of Renal Perfusion and Filtration Fraction

Renal perfusion was qualitatively evaluated by monitoring the bolus of ^{99m}Tc-DTPA during the initial 60 s and interpreted according to the consensus of three board-certified nuclear medicine physicians (DYL, HJS, and SYC) as previously described [18, 22]. The glomerular filtration rate was also qualitatively evaluated by analyzing ^{99m}Tc-DTPA uptake during the 2–3 min period. The readers were blinded to the clinical data. However, they were informed of the kidney to be evaluated for perfusion and filtration fraction compared with those of the contralateral kidney. The subject kidney that showed an abnormal renogram or lower ^{99m}Tc-DTPA uptake was determined by investigators who had access to all available data. Then, the blinded readers evaluated the RFF, defined as the glomerular filtration rate during the 2 to 3-min period compared with the perfusion of the subject kidney during the first 60 s and scored from 1 to 5 (1 = definitely same, 2 = probably same, 3 = possibly decreased, 4 = probably decreased, and 5 = definitely decreased). The qualitative RFF was interpreted as abnormally decreased if the consensus score by two readers was 3 or higher. Any discrepancies were resolved by the third reader.

Renal perfusion was also quantitatively measured using the Syngo workstation (Siemens Healthcare) as the percentage of the peak count of the subject kidney to the total peak count of both kidneys during the initial 60 s as shown in Fig. 1. The RFF was calculated by dividing the relative glomerular filtration rate (the percentage of renal uptake of the subject kidney to the total renal uptake of both kidneys during the 2–3 min period) by the relative renal perfusion rate. The equation is as follows: quantitative RFF = {2–3 min uptake of subject kidney/(2–3 min uptake of right kidney + 2–3 min uptake of left kidney)}/{perfusion peak uptake of subject kidney/(perfusion peak uptake of right kidney + perfusion peak of left kidney)}.

Statistical Analysis

Data are expressed as the mean ± standard deviation for continuous variables or numbers (%) for categorical variables. A P value of < 0.05 was considered statistically significant. Inter-reader variability of qualitative RFF was evaluated using the kappa statistic. Statistical comparisons were performed by Mann-Whitney U and chi-square tests. The sensitivity and specificity of the qualitative and quantitative RFF for the diagnosis of RVHT were calculated with 95% confidence interval (CI). Receiver operating characteristic curve analysis was performed to evaluate the accuracy of the quantitative RFF in the diagnosis of patients with high probability for RVHT and to define optimal cutoff values. Statistical analysis was performed using MedCalc version 12.7.0.0 (MedCalc Software).

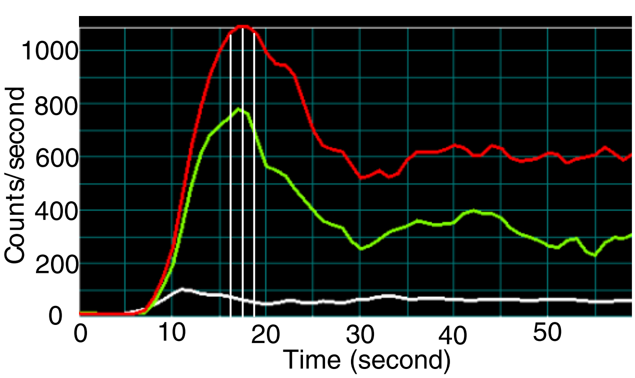

Fig. 1 Quantitative measurement of the relative renal perfusion by dividing the peak counts (white lines) of the reference kidney (green line) for 3 s during the dynamic perfusion phase by those of the contralateral kidney (red line)

Results

Patient Characteristics

Between March 2007 and December 2017, 224 patients underwent ^{99m}Tc-DTPA captopril renal scintigraphy and were assessed for eligibility. In total, 173 were finally included. Figure 2 shows the flowchart of the study. Based on scintigraphic findings, we identified 15 patients with high probability for RVHT and 158 patients with low probability. The baseline clinical characteristics of the patients are shown in Table 1. Of 15 patients with high probability, nine patients were confirmed to have significant renal artery stenosis by angiography, but the remaining six patients did not undergo angiography. The causes of renal artery stenosis assessed by conventional imaging were fibromuscular dysplasia ($n = 9$), Takayasu's arteritis ($n = 2$), atherosclerosis ($n = 2$), and embolism ($n = 1$). However, in one patient, no stenotic lesion was identified by magnetic resonance angiography. Of 158 patients with low probability, two patients underwent renal angiography, which revealed renal artery stenosis in one patient.

Qualitative Analysis

Table 2 shows the association between the probability for RVHT and the qualitative RFF assessed by standard interpretation criteria. Of 15 patients with high probability for RVHT, 12 patients had an abnormal qualitative RFF, and the diagnostic sensitivity of the RFF was 80.0% (95% CI, 51.9–95.7). The RFF was normal in 152 of 158 patients with low probability for RVHT, and the diagnostic specificity was 96.2% (95% CI, 91.9–98.6). Of 9 patients with angiographically confirmed renal artery stenosis, 7 patients (77.8%) had a positive qualitative RFF. Representative examples of decreased and normal RFF are shown in Figs. 3 and 4. The inter-reader agreement was 0.39 (95% CI, 0.19–0.58).

Quantitative Analysis

The quantitative RFF in patients with high and low probability for RVHT was 33 ± 10 and 44 ± 7, respectively, with a significant difference between both groups ($P < 0.0001$). The relative glomerular filtration rate after captopril administration was significantly lower in the high probability group than in the low probability group (27 ± 10 vs. 45 ± 5, $P < 0.0001$). Therefore, the RFF was lower in patients with high probability than in those with low probability (0.79 ± 0.15 vs. 1.02 ± 0.11, $P < 0.0001$; Fig. 5a). The RFF of nine patients with high probability and angiographic evidence of renal artery stenosis

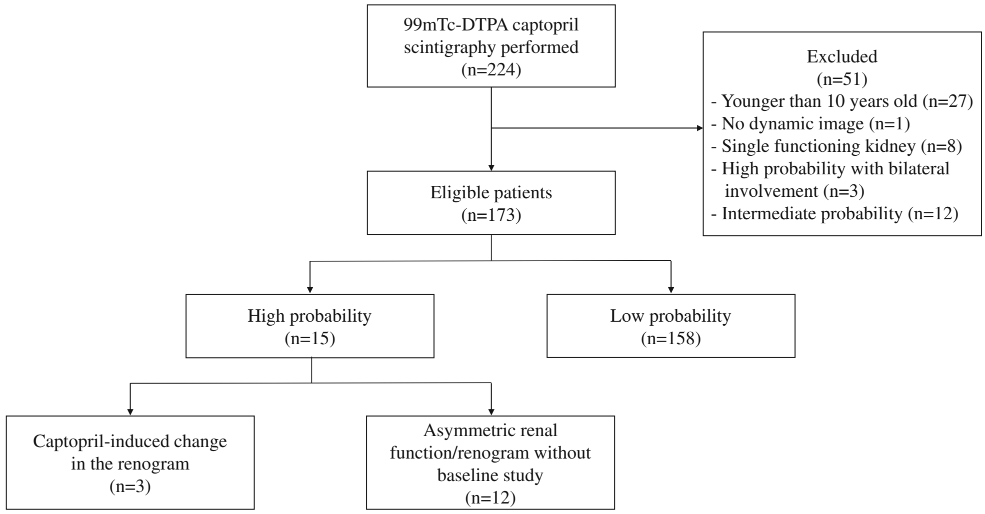

Fig. 2 Study schema

(0.86 ± 0.11) was also significantly lower than that of patients with low probability ($P < 0.0001$). The area under the receiver operating characteristic curve of the RFF for the diagnosis of patients with high probability for RVHT was 0.878 (95% CI, 0.834–0.933, $P < 0.0001$; Fig. 5b). The diagnostic sensitivity and specificity of the RFF were 66.7% (10/15; 95% CI: 38.4–88.2%) and 98.1% (154/158; 95% CI: 94.6–99.6%), respectively, with an optimal cutoff value of 0.81. Of 15 patients with high probability for RVHT, two patients had true positive qualitative RFF but false negative quantitative RFF. In these patients, the perfusion of the spleen overlapped with that of the contralateral left kidney (Fig. 6).

Discussion

This study was the first to investigate the value of the filtration fraction for the diagnosis of RVHT. The relative renal perfusion and RFF were assessed by analyzing dynamic flow images acquired during routine ^{99m}Tc-DTPA captopril renal scintigraphy. We demonstrated the high sensitivity and specificity of the qualitative and quantitative RFF assessed by ^{99m}Tc-DTPA captopril renal scintigraphy for the detection of patients with high probability for RVHT.

A decreased glomerular filtration rate or change in the renogram curve after ACE inhibition should be compared with baseline findings to differentiate RVHT from other diseases. For the 2-day protocol, captopril renal scintigraphy was performed on the first day. When the study is abnormal, a baseline study should be conducted to improve specificity [15]. However, clinicians may perform angioplasty without baseline renal scintigraphy. In these cases, the prediction of the response to revascularization may not be accurate. A decreased filtration fraction after ACE inhibition is a characteristic of RVHT. Therefore, a decreased RFF after ACE inhibition could be another criterion for selecting patients with functionally significant renal artery stenosis. The RFF might serve a complementary role when a baseline study is not available and increase reader's confidence.

The RFF demonstrated a high sensitivity for the detection of patients with high probability for RVHT. However, not all patients with high probability had a positive RFF. Previous studies have shown that renal perfusion is also reduced after ACE inhibition in cases of severe renal artery stenosis [14, 19]. Therefore, it is expected that the RFF will not decrease in these patients. A false negative RFF may indicate the presence of severe renal artery stenosis. Additionally, splenic perfusion overlapping with renal perfusion was the cause of false-negative quantitative RFF as shown in Fig. 6. Careful

Table 1 Characteristics of the 173 patients selected for analysis

Characteristic	High probability group ($n = 15$)	Low probability group ($n = 158$)	Total ($n = 173$)	P value
Age (years)	29 ± 15	28 ± 16	33 ± 16	0.46
Male sex (%)	7 (47%)	106 (67%)	119	0.52
Serum creatinine (mg/dL)	0.79 ± 0.26	0.90 ± 0.64	0.98 ± 0.62	0.14
Glomerular filtration rate (mL/min/1.73 m^2)	106 ± 41	100 ± 50	107 ± 49	0.40

Table 2 Diagnostic accuracy of the qualitative RFF for the diagnosis of patients with high probability for RVHT assessed by ^{99m}Tc-DTPA renal scintigraphy with standard interpretation criteria after ACE inhibition

Qualitative RFF	Probability for RVHT		
	High	Low	Total
Decreased	12	6	18
Normal	3	152	155
Total	15	158	173

consideration of splenic perfusion should reduce false-negative results.

In this study, high probability of RVHT on captopril renal scintigraphy (the reference standard) was regarded as having RVHT. To evaluate the performance of the index test (RFF), we excluded patients whose captopril renal scintigraphy showed a small, or decreased functioning kidney without prolongation of the renal transit time on captopril renal scintigraphy (intermediate probability). Although, we did not evaluate RFF in patients with intermediate probability, RFF might be a useful index in these patients because RFF would rather increase in order to maintain glomerular filtration rate in most diseases other than RVHT.

The very high specificity of the RFF suggests that a decreased RFF supports the diagnosis of RVHT. A high specificity is important because the predictive value may be limited by a high prevalence of hypertension coupled with a low incidence of RVHT [23, 24]. To minimize false positive results, a decreased RFF should be interpreted considering the changes in the glomerular filtration fraction or renogram curve after ACE inhibition.

Currently, recommended diagnostic tests to aid in the screening for RVHT are renal scintigraphy after ACE inhibition, Doppler sonography, magnetic resonance angiography, and computed tomography [25, 26]. However, randomized clinical studies have failed to show an improved outcome of revascularization compared with medical therapy in patients with atherosclerotic RVHT [27, 28]. Physiologic determination to confirm the severity of renal hypoperfusion might improve the selection of patients who may benefit from renal artery revascularization [29]. Therefore, renal scintigraphy after ACE inhibition serves as a screening tool and may further identify patients who are likely to respond to revascularization. If RFF assessed by dynamic ^{99m}Tc-DTPA scintigraphy after ACE inhibition can accurately diagnose RVHT without baseline scintigraphy, renal scintigraphy after ACE inhibition would be a more convenient screening test that can be done in a single day and at the same time a physiological test to assess RVHT.

There are several limitations in this study. First, this was a retrospective study using a small number of patients with high probability for RVHT, which could limit statistical analysis. Furthermore, we could not enroll patients who did not undergo ^{99m}Tc-DTPA captopril renal scintigraphy. This study does not represent all eligible patients. However, it is likely that this study did not make inappropriate exclusion of difficult-to-diagnose patients because patients with apparent RVHT usually undergo angiography without other tests, but patients who are more difficult to diagnose clinically are often subjected to

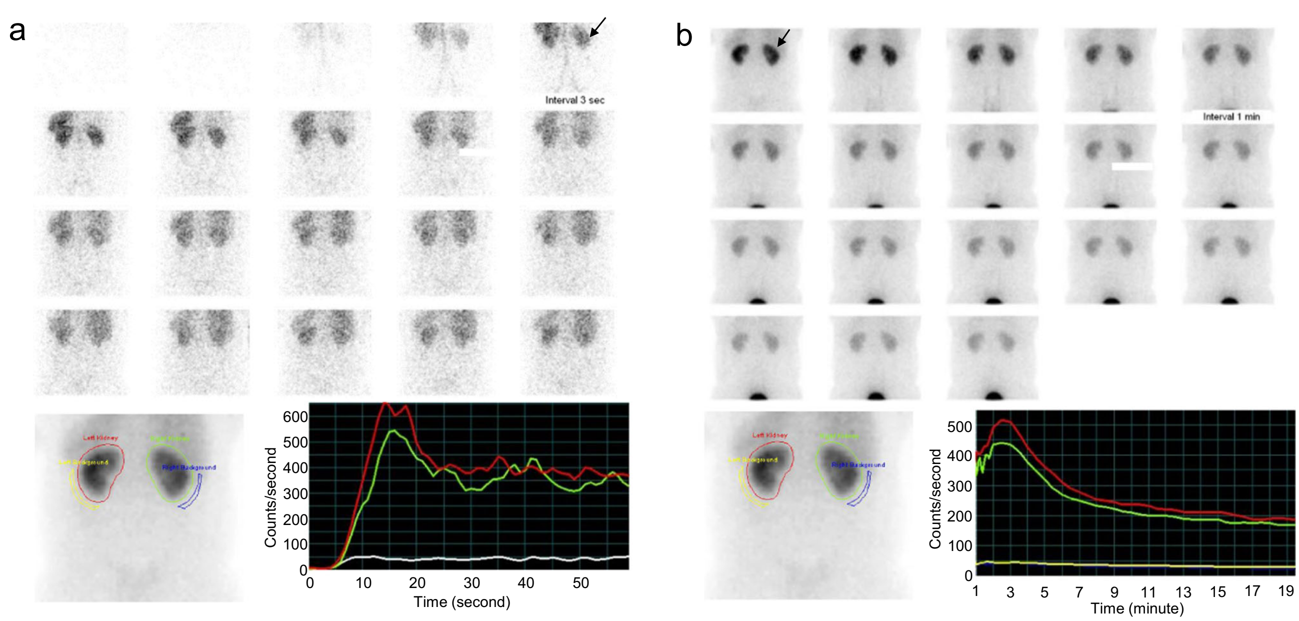

Fig. 3 ^{99m}Tc-DTPA captopril renal scintigraphic images of a 21-year-old male with hypertension showing **a** normal renal perfusion and **b** normal glomerular filtration in both kidneys, which indicated a low probability for renovascular hypertension (RVHT). The quantitative RFF of the reference right kidney was 1.0 (arrows). Red—left kidney, green—right kidney, yellow and blue—background, and white—aorta

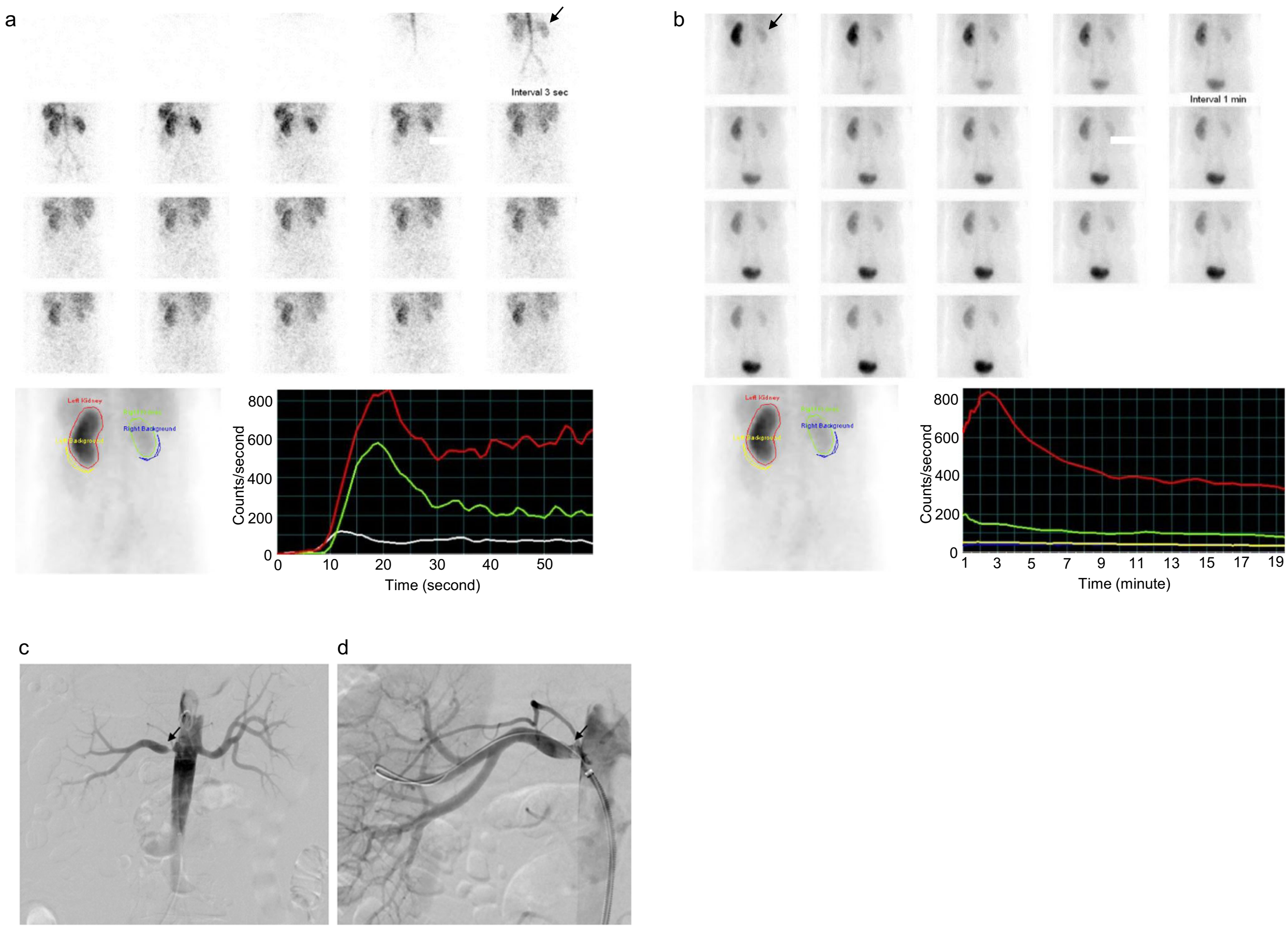

Fig. 4 ^{99m}Tc-DTPA captopril renal scintigraphic images of a 49-year-old female with hypertension showing **a** normal renal perfusion but **b** severely decreased glomerular filtration in the right kidney (arrows), which indicated a high probability for RVHT. The RFF of the right kidney was interpreted as abnormally decreased. The quantitative RFF was 0.55. **c** Angiography confirmed severe stenosis of the right renal artery due to fibromuscular dysplasia (arrow). **d** Percutaneous transluminal angioplasty was performed (arrow), and the blood pressure was improved after angioplasty. Red—left kidney, green—right kidney, yellow and blue—background, and white—aorta

^{99m}Tc-DTPA captopril renal scintigraphy. The selection of patient would not have introduced bias in the favorable direction. Despite the small number of patients, we obtained significantly different RFF values between patients with high and low

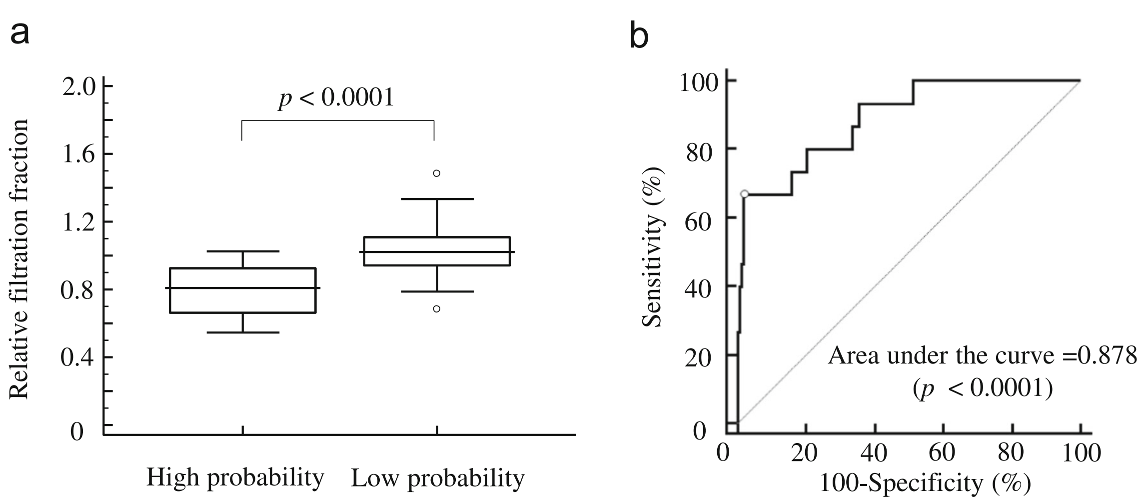

Fig. 5 **a** Box-whisker plot showing the quantitative RFF of patients with high and low probability for RVHT. **b** The area under the receiver operating characteristic curve demonstrated the high accuracy of the quantitative RFF

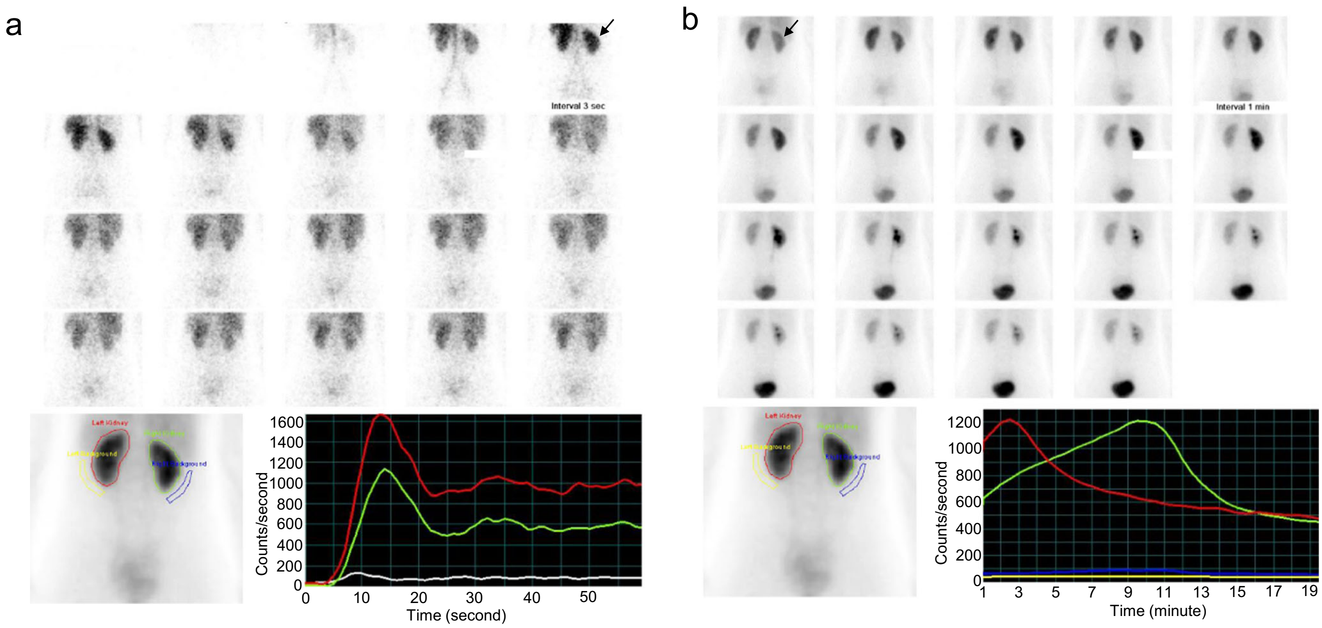

Fig. 6 **a**, **b** ^{99m}Tc-DTPA captopril renal scintigraphic images of a 21-year-old female with hypertension showing mildly decreased glomerular filtration in the right kidney and a marked delay in excretion with preserved washout phase (high probability for RVHT). The qualitative RFF of the right kidney was interpreted as abnormally decreased; however, the quantitative RFF was 0.96. Overlapped spleen activity within the region of interest of the left kidney might have resulted in the overestimation of the RFF of the right kidney. Red—left kidney, green—right kidney, yellow and blue—background, and white—aorta

probability for RVHT. Second, of 15 patients with high probability for RVHT, 12 patients did not undergo baseline ^{99m}Tc-DTPA renal scintigraphy despite abnormal captopril renal scintigraphy. Patients with marked unilateral delayed excretion accompanied by a reduction in the relative uptake (greater than 20% compared with the contralateral kidney) were regarded as having a high probability. This criterion for unilateral kidney involvement was found to predict normalized blood pressure after revascularization in our previous study [20]. Furthermore, all nine patients who underwent angiography were confirmed to have renal artery stenosis, and their qualitative and quantitative RFF values were abnormally decreased. Third, conventional interpretation of captopril renal scintigraphy was the reference standard in this study. Patients with high or low probability for RVHT were included. Therefore, we are not able to demonstrate additional benefit provided by RFF in this study. RFF is only a complementary diagnostic index and may be useful in differential diagnosis of decreased glomerular filtration rate after ACE inhibition when baseline scintigraphy is not available. Finally, an inter-reader agreement was fair. However, we believe that discordance may be due to no prior experience of the blinded readers in RFF interpretation. We had no educational cases for training blinded readers because we included all patients. Highly significant difference of quantitative RFF between patients with high and low probability suggests that reproducibility of qualitative RFF will improve with more experience.

Conclusion

The RFF assessed by dynamic ^{99m}Tc-DTPA scintigraphy after ACE inhibition can accurately detect patients with high probability for RVHT. With a very high specificity, an abnormal RFF may support the diagnosis of RVHT. The RFF after ACE inhibition might be a useful diagnostic criterion especially when baseline scintigraphy is not available for the evaluation of ACE inhibition-induced changes. Our retrospective results require further confirmation in a larger cohort with angiography or improved blood pressure as a reference standard.

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Compliance with Ethical Standards

Conflict of Interest Eonwoo Shin, Hye Joo Son, Dong Yun Lee, Sun Young Chae, and Dae Hyuk Moon declare that they have no conflict of interest.

Ethical Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed Consent The institutional review board at our institute approved this retrospective study, and the requirement to obtain informed consent was waived.

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