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Likelihood Ratios in the Diagnosis of Renal Artery Stenosis by Magnetic Resonance Angiography Compared With Renal Angiography

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Joseph Musial, and Raviprasenna Parasuraman

Background: Renal angiography (RA) is considered to be the gold standard for the diagnosis of renal artery stenosis (RAS). However, it is invasive and potentially harmful; hence there is a need for an optimal noninvasive test. Magnetic resonance angiography (MRA) is currently accepted as the optimal noninvasive test by many. However, its major drawback is its inability to grade quantitatively the degree of stenosis. In this study, likelihood ratios (LR) were used to compare the diagnostic accuracy of MRA with that of RA.

Methods: To test the hypothesis that semiquantitatively graded MRA would correlate with RA, a retrospective analysis was performed to determine the LR of MRA to diagnose RAS compared with RA. It was believed that LR ≥ 10.0 or ≤ 0.1 might generate conclusive changes from pretest to post-test probabilities. In this study a total of 94 renal arteries from 48 patients were analyzed for RAS by MRA and RA. Stenoses were graded by MRA as mild

(<50%), moderate (50% to 75%), or severe (>75%); and by RA as <75% or $\geq 75\%$ stenosis.

Results: The LR was 0.13 (95% CI = 0.09 to 0.19) for mild stenosis, 0.11 (95% CI = 0.08 to 0.15) for moderate stenosis, and 2.2 (95% CI = 1.9 to 3.1) for severe stenosis by MRA.

Conclusions: Nonsevere stenosis can be sufficiently diagnosed by MRA and may not warrant RA. However, it may be insufficiently precise to establish severe RAS based on LR results. Therefore, for severe RAS by MRA, the decision to obtain RA can be made with the help of post-test probability, which is determined using pretest probability and LR. Am J Hypertens 2003;16:987-992 © 2003 American Journal of Hypertension, Ltd.

Key Words: Renal artery stenosis, renal angiography, magnetic resonance angiography, likelihood ratio.

P rimary disorders of the renal arteries typically involve the large renal arteries, whereas secondary disorders more frequently affect smaller arteries and intrarenal vessels. Renal artery stenosis (RAS), attributable to fibromuscular dysplasia (FMD) or atherosclerosis, represents an important cause of secondary hypertension and ischemic nephropathy. The disease of FMD comprises a collection of disorders that variably affect the intima, media, or adventitia of the vascular tree. This group accounts for nearly 10% of the cases of RAS and is classically diagnosed in female individuals 15 to 50 years of age. Typical sites of involvement are the distal two thirds of the renal artery and its branches with beaded aneurysmal dilatations. The treatment of FMD has included angioplasty with or without stenting, or surgical correction of the stenotic lesions.^{1,2}

Atherosclerotic RAS accounts for 90% of cases, and usually involves the ostium and the proximal third of the renal artery. The incidence of this problem increases with age, particularly in patients with diabetes, hypertension, or aorto-occlusive or coronary artery disease.³

Although renovascular hypertension may accelerate or induce malignant hypertension, it is not readily distinguishable clinically from essential hypertension.³ Persons with the classical features of hypokalemia, abdominal bruit, an absence of a strong family history of hypertension, duration of hypertension of <2 years, and the onset of hypertension after the age of 50 years are more likely to have renovascular hypertension than other causes of hypertension, but none has sufficiently strong positive predictive value to diagnose atherosclerotic RAS readily.³

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Table 1. Demographic characteristics of 48 patients with suspected renal artery stenosis

Gender	Male (22)	Female (26)
Ethnicity	White (24)	African American (24)
Diabetes	Yes (17)	No (31)
Hypertension	<2 y (47)	>2 y (1)
Currently smoking*	Yes (29)	No (19)
Vascular disease†	Yes (33)	No (15)
Aortic aneurysm	Yes (6)	No (42)

Data are numbers of patients. Description of patient demographics. The average blood pressure for the patients was 193/108 mm Hg. The average serum creatinine and BUN were 1.9 (1.4 to 2.6) mg/dL and 21 (15 to 26) mg/dL, respectively. The average number for blood pressure medications that were used by the patients was 3.6. The mean pretest probability score was 13, which would correlate on the prediction rule curve with 48%.

* The average smoking history for the 29 patients was 16 packs-year.

† Vascular diseases include coronary artery disease (28 patients), peripheral vascular disease (9 patients) and carotid artery disease (11 patients). Some patients had more than one vascular disease at the same time.

Measurement of pressure gradient benefit after revascularization is considered to be the gold standard for diagnosing hemodynamically significant RAS in patients who undergo angioplasty with or without stenting of renal artery.⁴ Renal artery angiography is presently the alternative standard modality for diagnosing this condition before revascularization; however, it is invasive and has significant complications. Clinically, patients with suspected RAS can be categorized into three risk groups (ie, low, moderate and high risk) as described by Mann et al.⁵ Despite the fact that the final confirmation of the presence of RAS can be done only by RA, accurate delineation of those with moderate risk for RAS is necessary to avoid inappropriate invasive angiography and its complications. The noninvasive test of choice at present seems to be MRA. Besides the anatomical evaluation of the renal artery, MRA can provide information about hemodynamic significance by evaluating the flow, kidney size, symmetry of enhancement, and poststenotic dilatation. However, several other modalities to evaluate RAS have been used to varying degrees, including measurements of plasma renin activity, captopril renal scintigraphy, intravenous pyelography, nuclear imaging with diethylenetriamine-pentaacetic acid and duplex ultrasonography. Each of these has its limitations, unfortunately; but most importantly, their sensitivities and specificities are generally too low to be universally recommended.⁶

To circumvent in part the shortcomings of the other modalities and to avoid the complications of renal angiography, we adopted the use of LR in the diagnosis of RAS by MRA in comparison with RA by applying a previously described technique.^{7,8,9} Subsequently, LR was used to convert the pretest probability of RAS (based on prediction rule) to a post-test probability of RAS, which can help to identify those patients who require RA.

Methods

The hospital institutional review board approved the research protocol and methods. All patient data were obtained from the medical record database of our tertiary

hospital (an urban-based, 903-bed, academic tertiary care facility). This is a pure imaging comparison study that included any patient ≥ 50 years old with a moderate risk of having RAS (moderate hypertension [diastolic blood pressure > 105 mm Hg] that was associated with abdominal bruit and was refractory to medical therapy (using three or more antihypertensive medications including a diuretic with at least another two classes of antihypertensive medications) and stable kidney function for > 6 months. The patients who had acute renal failure, end-stage renal disease, fibromuscular dysplasia, or recent intervention for RAS were excluded from the study. Patient characteristics are presented in Table 1.

A total of 94 renal arteries (N = 48 patients; two unilateral nephrectomies) were retrospectively analyzed for stenosis by both techniques. All patients had undergone MRA and renal angiography between July 1, 1997, and June 30, 2000, for evaluation of possible renovascular disease. The mean age of the patients was 59 ± 8 years. The interval between the two tests was 3 days on average. The indication for testing was refractory hypertension with three or more antihypertensive medications (including a diuretic with at least another two classes of antihypertensive medications) and no overt clinical features of any other cause of secondary hypertension. None of the patients had any functional evaluation of the renin-angiotensin system. Both tests were performed for all the patients because the primary team or the primary care physician who was taking care of the patients was ordering the MRA, whereas the nephrologists, when consulted, were ordering the RA.

The MRA studies were conducted with a 1.5 tesla superconducting unit (General Electric Medical Systems, Signa 1.5T Horizon Platform, Voorhees, NJ), using a three-dimensional gradient-echo sequence and a rapid low-angle shot with a repetition time of 3.8 msec. An unenhanced study was acquired as a reference scan before administration of radiocontrast. A 25-mL bolus of intravenous⁵⁷ Gd was followed by 25 mL of normal saline. After a 15-second breath-holding interval, a contrast-en-

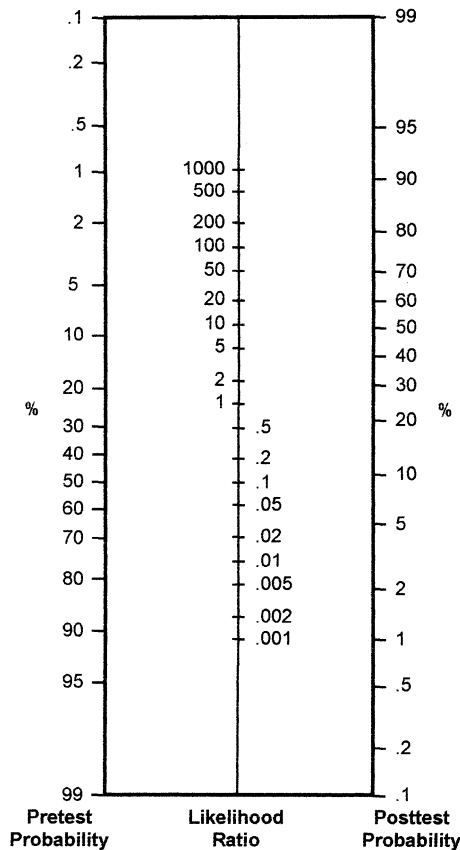


FIG. 1. Nomogram illustrating how to calculate post-test probabilities from likelihood ratios. The extension of a line that connects the pretest probability to the likelihood ratio (LR) will yield the post-test probability. For example, if the clinical scenario of a patient with renal artery stenosis in question suggests a pretest probability of 50% and the MRA demonstrates moderate stenosis, then the post-test probability will be 10%; in this study the LR for moderate stenosis by MRA is 0.11. (Adapted from Reference 9, with permission).

hanced MRA was performed during a 30-sec breath-holding period. Angiographic studies were conducted in the conventional manner by means of femoral percutaneous cannulation. All the patients had flush aortography. Selective renal angiography is not performed and oblique views are not obtained routinely because the reconstruction of the images by the computer provides enough information. However, when visualization is incomplete, a selective renal angiogram is obtained with two oblique views (right anterior oblique [RAO] and left anterior oblique [LAO]). Pressure gradients are not measured routinely unless revascularization is performed.

Briefly, the technique was as follows. Approximately 30 mL of meglumine diatrizoate was injected into each renal artery. A radiologist experienced in MRA read the MR angiographies, and an independent experienced interventional radiologist read all of the renal angiograms. Stenoses were graded by MRA as mild (<50%), moderate (50% to 75%), or severe (>75%). Subjective evaluation of flow, kidney size, symmetry of enhancement, and poststenotic dilatation was done by the radiologist and that was

considered in grading the stenosis. Spin dephasing on the computer was not done. By RA, stenoses were categorized as <75% or ≥75%. These degrees of stenosis were chosen based on previous studies.^{6,10-14} Although severe RAS by RA or MRA does not necessarily equal clinically significant RAS, they are practically considered to be equal.^{3,15}

The following statistical analyses were generated: 1) basic group descriptive statistics, including mean, median, and SD; and 2) likelihood ratios to ascertain the diagnosis of RAS at different levels of stenosis in MRA and RA. Statistical analyses were conducted with SPSS, version 10.01 software (SPSS Inc., Chicago, IL).

The LR for mild and moderate stenosis was calculated by the formula: $LR = 1 - \text{sensitivity}/\text{specificity}$, as mild and moderate stenoses were considered to be clinically insignificant (negative) results. The LR for severe stenosis was calculated by the formula: $LR = \text{sensitivity}/(1 - \text{specificity})$, as severe stenosis was considered to be a significant (positive) result.

The LR modifies the pretest probability of a given diagnostic test for a suspected disorder. A value of $LR = 1.0$ indicates that the post-test probability of a suspected disorder has not changed from its pretest probability. A value of $LR < 1.0$ indicates a decrease and $LR > 1.0$ indicates an increase in the post-test probability of the target disorder. Moreover, $LR \geq 10.0$ or ≤ 0.1 generate large and often conclusive changes from pretest to post-test probabilities. Values of LR of 5.0 to 10.0 and of 0.1 to 0.2 generate moderate revisions of the pretest probability, whereas LR of 2.0 to 5.0 and 0.5 to 0.2 represent smaller but occasionally important alterations in the pretest probability. Likelihood ratios from 1.0 to 2.0 and from 0.5 to 1.0 are generally clinically unimportant.^{7,8}

Post-test odds were calculated by multiplying the pretest odds ratio (OR) by the calculated LR. Pretest OR were calculated from pretest probabilities as follows: $\text{Pretest OR} = \text{Pretest Probability}/[1 - \text{Pretest Probability}]$. The post-test odds can be converted to probabilities by the equation: $\text{Probability} = \text{Odds}/[\text{Odds} + 1]$. Post-test probability can also be determined from the LR and the pretest probability using the nomogram of Fagan as shown in Fig. 1.⁹

Results

In an examination of 94 renal arteries from 48 patients with suspected RAS, MRA revealed mild stenosis in 20 renal arteries, moderate stenosis in 16, and severe stenosis in 58 (Table 2). The RA disclosed <75% stenosis in 51 arteries and ≥75% stenosis in 43 arteries. Data on the location of the stenosis was not collected. A total of 18 arteries with mild stenosis by MRA had <75% stenosis by RA. Only two arteries with mild MRA-demonstrable stenosis had ≥75% stenosis by RA. These results yielded an LR of 0.13 (95% CI = 0.09 to 0.19) when MRA was considered as mild. Thirteen arteries were categorized moderately stenotic by MRA and <75% stenotic by RA,

Table 2. Results of renal angiography and magnetic resonance angiography in 94 renal arteries from 48 patients with suspected renal artery stenosis

	RAS <75%	RAS ≥75%	Total	LR (95% CI)
Mild MRA	18	2	20	0.13 (0.09–0.19)
Moderate MRA	13	3	16	0.11 (0.08–0.15)
Severe MRA	20	38	58	2.2 (1.9–3.1)
Total	51	43	94	

Data are numbers of patients. Description of the results of the two diagnostic modalities and the calculated likelihood ratios (LR) with 95% CIs. Two independent radiologists determined the level of stenosis in both the MRA and the RA. For calculation of LR, refer to Methods.

LR = likelihood ratio; MRA = magnetic resonance angiography; RAS = renal artery stenosis.

whereas three arteries that were moderately stenotic by MRA, had ≥75% stenosis by RA. These data yielded a LR of 0.11 (95% CI = 0.08 to 0.15) when MRA was described as moderate. However, from a total of 58 arteries, 20 arteries with known severe stenosis by MRA had <75% angiographically proven stenosis, whereas 38 arteries with severe stenosis by MRA had ≥75% angiographically proven stenosis. These data yielded a LR of 2.2 (95% CI = 1.9 to 3.1) when the MRA was graded as severe.

Discussion

The technique of MRA has rapidly evolved as the noninvasive diagnostic method of choice for RAS; it is not associated with any of the significant complications of angiography, which include hemorrhage, infection, atheroembolism, and acute renal failure. However, noninvasive diagnosis of RAS is challenging.^{6,9,15} Overall, MRA has an sensitivity of 93% and a specificity of 83% for the diagnosis of RAS with lesions graded ≥50%. Classification of stenosis by MRA is generally semiquantitatively graded as mild, moderate, or severe. Angiographic lesions are usually expressed as clinically significant (≥75% occlusion) or insignificant (<75% occlusion).^{11,12,16,17} We subsequently elected to translate the semiquantitative terminology applied to MRA to the quantitative RA through the application of LR.

After determining the LR for a given test, it is combined with its pretest probability to calculate a post-test probability. Importantly, the pretest probability cannot be directly used to calculate the LR but first requires conversion to an OR. However, post-test probabilities can easily be determined with the previously described nomogram of Fagan,⁹ which conveniently determines post-test probability from the product of pretest probability and the calculated LR.

The pretest probability can be determined based on a previously described prediction rule for patients with suspected RAS.¹⁸ In the prediction rule for RAS, a score is assigned to the level or presence of each clinical characteristic in Table 3. These scores are added into a sum score. The results of the prediction rule may not be reproducible from one center to another because of different

patterns of drug therapy leading to different patterns of response. This is especially important when using diuretics to treat unilateral RAS, inasmuch as these agents will not control blood pressure and may subsequently make anti-renin therapy less effective by depleting the intravascular volume and increasing renin level. However, our patients had similar characteristics to the those of the prediction rule study patients. In Fig. 2, the predicted probabilities can be derived from the sum scores in a graphic manner. For instance, the sum score for a 49-year-old woman who had smoked in the past, has no signs or symptoms of atherosclerotic vascular disease, received a diagnosis of hypertension 1 year previously, and has a body mass index of 22 kg/m², no abdominal bruit, a serum creatinine concentration of 101 μmol/L (1.11 mg/dL), and a serum cholesterol level of 5.4 mmol/L (208.82 mg/dL), and does not take cholesterol-lowering drugs is 13 (5 + 2 + 0 + 1 + 2 + 0 + 3 + 0). Figure 2 shows that the predicted probability of RAS in this patient is 50%. If her doctor proceeded with MRA and if bilateral moderate stenosis was detected, the physician would subsequently conclude from the nomogram that the post-test probability for RAS was only 10%. This calculation would be predicated upon the determination that the LR in for this set of parameters was 0.11 (Table 2). Therefore, in this particular circumstance, a more extensive and costly evaluation such as renal arteriography would be much less warranted.

In this retrospective analysis, MRA was performed for suspected RAS. In cases of mild to moderate RAS diagnosed by MRA, 31 of the 35 (89%) arteries evaluated were angiographically confirmed to have mild or moderate stenosis. In cases of severe RAS diagnosed by MRA, only 38 of 58 (65%) arteries evaluated, were subsequently established to have >75% stenosis by RA, consequently producing a high false-positive rate by MRA. Although there is no definite explanation for this observation, several factors may have produced this high false-positive rate with a resultant lack of specificity: 1) there is interobserver variability; 2) studies may be interpreted differently when there is kinking of the renal arteries and reconstruction artifact; and 3) MRA lacks the spatial resolution for adequate visualization of accessory renal arteries (for instance, when severe RAS was diagnosed by MRA, 13

Table 3. Prediction rule for quantifying the probability of renal artery stenosis

Predictors	Score*	
	Persons Who Never Smoked	Former or Current Smokers
Age, y†		
20	0	3
30	1	4
40	2	4
50	3	5
60	4	5
70	5	6
Female sex	2	2
Signs and symptoms of atherosclerotic vascular disease‡	1	1
Onset of hypertension within 2 y	1	1
Body mass index <25 kg/m ²	2	2
Presence of abdominal bruit	3	3
Serum creatinine concentration		
40 μmol/L (0.44 mg/dL)	0	0
60 μmol/L (0.66 mg/dL)	1	1
80 μmol/L (0.88 mg/dL)	2	2
100 μmol/L (1.1 mg/dL)	3	3
150 μmol/L (1.65 mg/dL)	6	6
200 μmol/L (2.2 mg/dL)	9	9
Serum cholesterol level >6.5 mmol/L (251.36 mg/dL) or lipid lowering agent	1	1

* The sum score is obtained by adding all relevant scores. The sum score can be used to obtain the predicted probability of RAS from Fig. 2.

† For intermediate values, the score can be linearly interpolated.

‡ Femoral or carotid bruit, angina pectoris, claudication, myocardial infarction, cerebrovascular accident, or vascular surgery.

Adapted from Krijnen et al.: A clinical prediction rule for renal artery stenosis. *Ann Intern Med* 1998;129:705-711, with permission.

errors were made in the case of accessory arteries and seven errors in the case of main arteries).^{13,17,19}

Because this is a retrospective analysis, a functional evaluation of the renin-angiotensin system or fractional flow to each kidney could not be accomplished, and this may have an impact on the calculation of LR in the diagnosis of RAS. Using any of the different modalities to evaluate the renovascular function, such as ACE inhibitor renography or scintigraphy, and the renal resistive index at Doppler ultrasonography in patients with suspected RAS,

will definitely enhance the capability of clinicians to determine the significance and the severity of RAS. This will also be very useful in predicting favorable response to revascularization.^{3,5,6}

In conclusion, in patients with moderate clinical index of suspicion for RAS, MRA seems to be sufficient to diagnose mild to moderate RAS (<75% stenosis) and may preclude performance of RA in these circumstances, inasmuch as LR in this situation will make huge changes in the probability of having the disease. However, MRA does not definitively establish severe RAS (≥75% stenosis). In this situation, the post-test probability can be calculated using LR and pretest probability from the prediction rule,¹⁸ which can facilitate decision making with regard to whether to proceed with RA in suspected cases of RAS. Therefore RA may not be necessary for all MRA-diagnosed cases of severe RAS. We recommend that screening for RAS with MRA should be combined with LR, and use of pretest probability from the prediction rule to facilitate the decision making process about whether to proceed with RA. Larger prospective and controlled studies are required to confirm these findings.

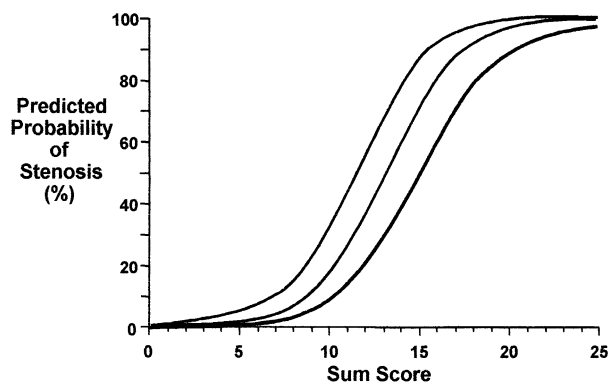


FIG. 2. The sum score was derived from the prediction rule. **Thin lines** represent 95% confidence intervals. (Adapted from Reference 18, with permission.)

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