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Screening for Primary Aldosteronism in Essential Hypertension: Diagnostic Accuracy of the Ratio of Plasma Aldosterone Concentration to Plasma Renin Activity

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Background: **The ratio of plasma aldosterone concentration to plasma renin activity (PRA) is considered the screening test of choice for primary aldosteronism. Uncertainty exists, however, regarding its diagnostic accuracy and the effects of antihypertensive drugs and dietary sodium balance on test characteristics.**

Methods: **We measured PRA and aldosterone in 118 white adults [71 men and 47 women; mean (SD) age, 51 (7) years] with previously diagnosed essential hypertension. Measurements were made while individuals were on antihypertensive drug therapy, after a 2-week drug-free period, after 4 days of dietary sodium loading, and after acute furosemide diuresis. We measured 24-h urine aldosterone excretion and PRA on the 4th day of dietary sodium loading to establish the diagnosis of primary aldosteronism. ROC curves were constructed for ratios measured under each clinical condition, and likelihood ratios were determined for individuals on or off antihypertensive drug therapy.**

Results: **Fifteen patients [13%; 95% confidence interval (CI), 7–20%] met the reference standard for primary aldosteronism. The mean (SD) areas under the ROC curves did not differ significantly across conditions of measurement [range, 0.80 (0.10) to 0.85 (0.04); $P = 0.72$]. When measured on and off antihypertensive drug therapy, the 95% CIs for the optimum cutpoint for the ratio overlapped. Point estimates of sensitivity on and off therapy were 73% (95% CI, 50–96%) and 87% (70–100%), respectively, and specificities were 74% (65–83%) and 75% (66–84%). Under either condition, increased ratios were associated with 2.4- to 13-fold increases of posttest odds above pretest odds.**

Conclusions: **The aldosterone:PRA ratio provides only fair diagnostic accuracy in screening for primary aldosteronism, but concomitant antihypertensive drug therapy or acute variation in dietary sodium balance does not adversely affect test accuracy. Reporting of likelihood ratios associated with ranges of values of the aldosterone:PRA ratio, rather than use of a single "optimum" cutpoint, may enhance the usefulness of the test.**

Recently published series suggest that primary aldosteronism is the most common secondary form of hypertension with prevalence estimates as high as 18% *(1–8)*. Moreover, some experts advocate screening of all hypertensive individuals for this disorder to guide drug selection and improve treatment success *(8, 9)*.

In 1976, Dunn and Espiner *(10)* first suggested simultaneous measurement of plasma aldosterone concentration and plasma renin activity (PRA)[1] and calculation of the aldosterone:PRA ratio as a potentially useful screening test for primary aldosteronism. They reasoned that because primary aldosteronism is characterized by increased aldosterone with consequent extracellular volume expansion and suppression of PRA, individuals with the disorder should have higher values of the ratio than those with essential hypertension. In 1981, Hiramatsu et al. *(11)* proposed the aldosterone:PRA ratio as the screening test of choice for primary aldosteronism. Currently, the ratio is widely accepted as a simple and reliable screening test for this disorder *(12, 13)*; however, its sensitivity and specificity have not been determined in individuals with

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[1] Nonstandard abbreviations: PRA, plasma renin activity; GCRC, General Clinical Research Center; and CI, confidence interval.

presumed essential hypertension, in whom the reference standard was performed subsequent to the screening test, regardless of the result of the latter test *(14)*. Moreover, experts do not agree on the clinical conditions for screening. In particular, although it is recognized that concomitant antihypertensive drug therapy can influence ratio values *(15)*, the effect on the diagnostic accuracy of the test has not been formally assessed. In addition, the influence of variation in dietary sodium balance on the diagnostic accuracy of the ratio is unknown.

The primary objective of this study, therefore, was to determine the sensitivity and specificity of the aldosterone:PRA ratio to screen a community-based sample of adults with presumed essential hypertension for primary aldosteronism based on the results of a urinary aldosterone suppression test as the reference standard. A second objective was to assess the overall influence of antihypertensive drug therapy and variation in dietary sodium balance on diagnostic accuracy of the ratio.

Materials and Methods

PARTICIPANTS

The sample of 118 individuals for the present study was recruited from a population-based cohort of 280 unrelated non-Hispanic white adults (122 women and 158 men; age range, 30–59.9 years) from Rochester, MN who had essential hypertension and had participated in a previous study to assess genetic predictors of blood pressure response to diuretic therapy *(16, 17)*. The present study was carried out from January 2000 through May 2002 with recruitment extending from January 2000 through February 2002. The parent cohort of 280 individuals was originally recruited from a list of all residents of Olmsted County, MN with the diagnosis of essential hypertension who had been seen by a healthcare provider in the previous 3 years before recruitment *(18)*. Candidates for the parent study who responded favorably to an informative letter about this study were recruited. Essential hypertension was defined as a blood pressure ≥140/90 mmHg or a previous diagnosis of essential hypertension and current use of prescription antihypertensive medications. Candidates were considered ineligible for the parent study for the following reasons: known or suspected secondary hypertension; unexplained hypokalemia; use of more than three antihypertensive medications for blood pressure control; allergy to hydrochlorothiazide; inability to discontinue antihypertensive medications; use of nonsteroidal antiinflammatory medications, including daily aspirin >325 mg; congestive heart failure; liver or renal disease (serum creatinine concentration >15 mg/L); or diabetes mellitus, defined as fasting blood glucose >1400 mg/L or taking hypoglycemic medications. Women taking oral contraceptive medications were disqualified, but those receiving postmenopausal hormone replacement were allowed. Candidates with hypokalemia while taking diuretics were allowed to participate. Participants in the parent study had to have a diastolic blood pressure >90 mmHg after discontinuing antihypertensive drug therapy.

All 280 participants from the parent study were sent a letter providing information about the present study. Interested candidates who contacted the study center were considered for recruitment. History, physical examination, and routine laboratory tests were used in the parent study to exclude secondary hypertension and were repeated in the present study. Participants had to be able to discontinue antihypertensive medications and any drug that could influence the renin-angiotensin-aldosterone axis. Candidates found to have diuretic-induced hypokalemia were placed on oral potassium supplements at the time of enrollment. All participants were required to review and sign a written consent form. Of the 280 candidates, 140 agreed to participate and 119 completed the study protocol. One individual was excluded from the analysis because of noncompliance with the study diet. The Institutional Review Board of the Mayo Clinic approved all procedures involving study participants. All study procedures were carried out in the Mayo Clinic General Clinical Research Center (GCRC) in accordance with institutional guidelines.

STUDY PROTOCOL

Determination of the aldosterone:PRA ratio to screen for primary aldosteronism. PRA and aldosterone concentrations for calculation of the ratio were obtained for all study participants on four separate occasions: (*a*) at the screening and consent visit before discontinuation of antihypertensive drug therapy; (*b*) after a minimum 2-week drug-free period; (*c*) after 4 days of dietary sodium loading (urinary aldosterone suppression test); and (*d*) after acute furosemide diuresis. Throughout the study, participants ate their usual diet except for a 1-week period before acute furosemide diuresis when they were instructed in a 90 mmol/day sodium diet. Blood samples for measurement of PRA and aldosterone were obtained with individuals in the seated position after 5 min of rest. All samples were obtained at ~0800 except for samples after acute furosemide diuresis, which were obtained at ~1800 (6 h after the last dose of furosemide).

Reference standard for primary aldosteronism. After a minimum 2-week antihypertensive-drug-free period, and in a potassium-replete state, all study participants underwent a urinary aldosterone suppression test. They ingested a diet designed to provide a daily sodium intake of at least 250 mmol over 4 consecutive days. Each day, breakfast and dinner were eaten at the GCRC and a box lunch was provided. With breakfast and dinner, participants were required to also ingest two NaCl tablets (17 mmol sodium/tablet). After 3 days on the diet, participants began a 24-h urine collection for measurement of sodium, potassium, creatinine, and aldosterone excretions. At ~0800 the next morning, blood was obtained after 5 min in the sitting position for measurement of sodium, potassium,

and aldosterone concentrations and PRA. For dietary sodium loading to be considered sufficient to suppress aldosterone, 24-h urinary sodium excretion was required to be ≥200 mmol. Under these conditions, a 24-h urinary aldosterone excretion ≥12 μg is consistent with autonomous aldosterone production and primary aldosteronism *(19)*.

Acute furosemide diuresis. Immediately after the urinary aldosterone suppression test, all study participants were instructed to ingest a 90 mmol/day sodium diet. After a minimum of 1 week on the diet, and in a potassium-replete state, they were subjected to acute furosemide-induced diuresis. Furosemide in a dose of 2 mg/kg of body weight was given orally at 0600, and the dose was repeated 6 h later at 1200. Before each dose, participants were weighed (beam balance), and blood pressures were measured after 5 min of quiet sitting and after 1 min of standing. Furosemide was given if systolic blood pressure was ≥120 mmHg, the change in systolic blood pressure from sitting to standing was <30 mmHg, and there were no complaints of lightheadedness. After each dose of furosemide, participants were allowed to engage in their usual daily activities but were instructed not to rest in the supine position. On the day of the test, all meals were ingested in the GCRC and fluid intake was restricted to 15 mL water/kg of body weight. Participants returned to the GCRC 6 h after the second dose of furosemide, at ~1800, when blood was obtained after 5 min in the sitting position for measurement of PRA and aldosterone, sodium, and potassium concentrations.

Laboratory procedures. Plasma and urine aldosterone was measured by RIA (Diagnostic Products Corporation). PRA was measured by RIA of angiotensin I in the presence of reagents that inhibit angiotensin I-converting enzyme and angiotensinases. The assay was performed according to the method of Sealy and Laragh *(20, 21)*, using GammaCoat Plasma Renin Activity RIA Kits (DiaSorin).

Each plasma and urine sample was assayed in triplicate, and the means were used in the analyses. For plasma aldosterone, the mean within- and between-assay CVs were 3.3% and 8.4%, respectively, for samples between 5.8 and 57.5 ng/dL.[2] For urine aldosterone, the mean within- and between-assay CVs were <7%. For PRA, the mean within- and between-assay CVs were 4.8% and 8.4%, respectively, for samples between 0.9 and 5.2 $ng \cdot mL^{-1} \cdot h^{-1}$.

Electrolyte concentrations were measured by use of an ion-selective electrode. Serum and urine creatinine concentrations were measured by automated spectrophotometric methods implemented on the Hitachi 911 Chemistry Analyzer (Roche Diagnostics).

[2] To convert aldosterone to SI units of pmol/L, multiply by 27.74; to convert PRA to SI units of ng/L · s, multiply by 0.2778.

All laboratory measurements were performed after participants completed the study protocol; therefore, study personnel were blinded to the results of the screening test and reference standard until the time of analysis.

STATISTICAL METHODS

The diagnostic criteria for primary aldosteronism, established before the study, were a 24-h urine aldosterone excretion ≥12 μg after dietary sodium loading (urine sodium excretion ≥200 mmol) and a concomitant PRA ≤1.0 $ng \cdot mL^{-1} \cdot h^{-1}$. At the end of the study, two individuals (the author and coauthor) who are trained nephrologists and experts in hypertension reviewed the laboratory results and determined who met the diagnostic criteria for primary aldosteronism without knowledge of the ratio values. The prevalence of primary aldosteronism and the 95% confidence intervals (CIs) were determined *(22)*.

Under each of the four clinical conditions, the aldosterone:PRA ratio was calculated for each participant. The ratio was calculated using conventional units for PRA ($ng \cdot mL^{-1} \cdot h^{-1}$) and aldosterone (ng/dL). To convert PRA to SI units of ng/L · s, multiply by 0.2778; to convert aldosterone to SI units of pmol/L, multiply by 27.74. In some publications, the ratio is calculated using aldosterone expressed in SI units and PRA expressed in conventional units. Dividing such values by 27.74 converts them to values used in the present analyses. Using the calculated aldosterone:PRA ratios, we generated ROC curves for the ratio under the four clinical conditions. We compared the area under each ROC curve for differences, using the method of Delong et al. *(23)*. The optimum ratio value for each clinical condition was defined as the value on the ROC curve that was associated with the minimum Euclidean distance (Pythagorean theorem) from the curve to the upper left corner of the graph, using the formula: $\sqrt{(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2}$. Bootstrapping was used to determine 95% CIs for each optimum ratio value. The sensitivity and specificity associated with the optimum ratio value for each clinical condition with its respective 95% CI were determined. Finally, for the two clinical conditions of screening most often encountered in clinical practice (on or off antihypertensive drug therapy), likelihood ratios for a positive test (sensitivity/1 − specificity) were determined for various ranges of ratio values. This is of practical value because it provides diagnostic information over the entire range of ratio values, rather than for only a single "optimum" cutpoint.

Results

DESCRIPTION OF THE SAMPLE

Of the 280 adults with previously diagnosed essential hypertension who were candidates for this study, 140 agreed to participate and 118 successfully completed the urinary aldosterone suppression test. Their median age was 52 years (range, 29–63 years), and 39.8% were women (n = 47). Other characteristics of the participants

Table 1. Description of the 118 study participants.[a]

Characteristic	Median	25th percentile	75th percentile	*P* (for normality)
Age, years	52	48	58	<0.010
Duration HT,[b] years	6	4	12	<0.010
BMI, kg/m^2	30.7	26.8	34.6	0.093
Systolic BP, mmHg	139	129	146	0.025
Diastolic BP, mmHg	91	87	97	>0.150
Sodium, mmol/L	142	140	144	>0.150
Potassium, mmol/L	4.5	4.3	4.7	>0.150
Creatinine, μmol/L	97	88	106	<0.010

[a] All measurements were obtained at the screening visit before study entry except for systolic and diastolic blood pressure, sodium, and potassium, which were measured when patients were off antihypertensive therapy before the urinary aldosterone suppression test.

[b] HT, hypertension; BMI, body mass index; BP, blood pressure.

are described in Table 1. Of the 118 participants, 113 (96%) were on antihypertensive drug therapy at study entry. Of these 113 individuals, 69 (61%) were on monotherapy and 44 (39%) were on combination therapy with two or three drugs. Sixty-two (55%) were on thiazide diuretics [25 of 62 (40%) on monotherapy]; 42 (37%) were on beta-blockers [19 of 42 (45%) on monotherapy]; 39 (35%) were on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [23 of 39 (59%) on monotherapy]; and 11 (10%) were on calcium antagonists [2 of 11 (18%) on monotherapy]. There were no adverse events associated with antihypertensive drug withdrawal, the aldosterone suppression test, or acute furosemide diuresis.

PREVALENCE ESTIMATE OF PRIMARY ALDOSTERONISM

Fifteen of the 118 participants [13% (95% CI, 7–20%)] met the reference standard for diagnosis of primary aldosteronism, i.e., PRA ≤ 1.0 ng · mL^{-1} · h^{-1} and 24-h urinary aldosterone excretion after dietary sodium loading ≥ 12 μg. Among those who met the diagnostic criteria for primary aldosteronism, median (range) 24-h urinary sodium excretion was 290 (201–494) mmol, median PRA was 0.40 (0.07–0.97) ng · mL^{-1} · h^{-1}, and median 24-h urinary aldosterone excretion was 14.9 (12.3–30.7) μg. Among participants who did not meet the diagnostic criteria for primary aldosteronism, the median (range) 24-h urinary sodium excretion was 302 (153–486) mmol, median PRA was 1.10 (0.06–4.66) ng · mL^{-1} · h^{-1}, and median 24-h urinary aldosterone excretion was 8.0 (1.5–24.7) μg.

DISTRIBUTION OF THE ALDOSTERONE:PRA RATIO IN THE STUDY SAMPLE

The distributions of ratio values for participants before and after discontinuation of antihypertensive drug therapy are shown in panels A and B, respectively, of Fig. 1. Under both clinical conditions, the ratio distribution was skewed to higher values among individuals with primary aldosteronism. In both diagnostic groups, discontinuation of antihypertensive drug therapy led to a shift of the distribution to higher values.

DIAGNOSTIC ACCURACY OF THE ALDOSTERONE:PRA RATIO

The ROC curves for the ratios under each clinical condition are displayed in Fig. 2. The diagnostic accuracy of the ratio, defined by the area under the ROC curve, did not differ significantly across clinical conditions [range of the mean (SD), 0.80 (0.10) to 0.85 (0.04); $P = 0.72$ for comparison].

OPTIMUM VALUES OF THE ALDOSTERONE:PRA RATIO AND ASSOCIATED TEST CHARACTERISTICS

Optimum values of the aldosterone:PRA ratio ranged from 8.9 mL/dL · h when measured after acute furosemide diuresis to 14.9 mL/dL · h when measured when

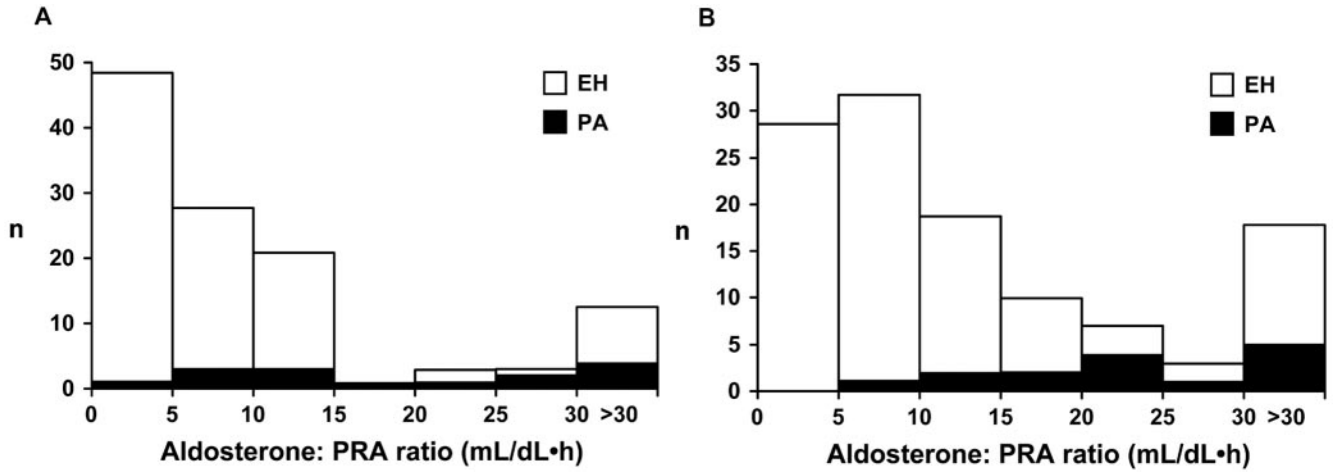

Fig. 1. Distribution of values for the ratio of plasma aldosterone concentration to PRA in the study sample by diagnosis of essential hypertension (*EH*) or primary aldosteronism (*PA*).

(*A*), distribution of ratio values in the study sample measured when participants were on antihypertensive drug therapy. (*B*), distribution of ratio values in the study sample measured when participants were off antihypertensive drug therapy.

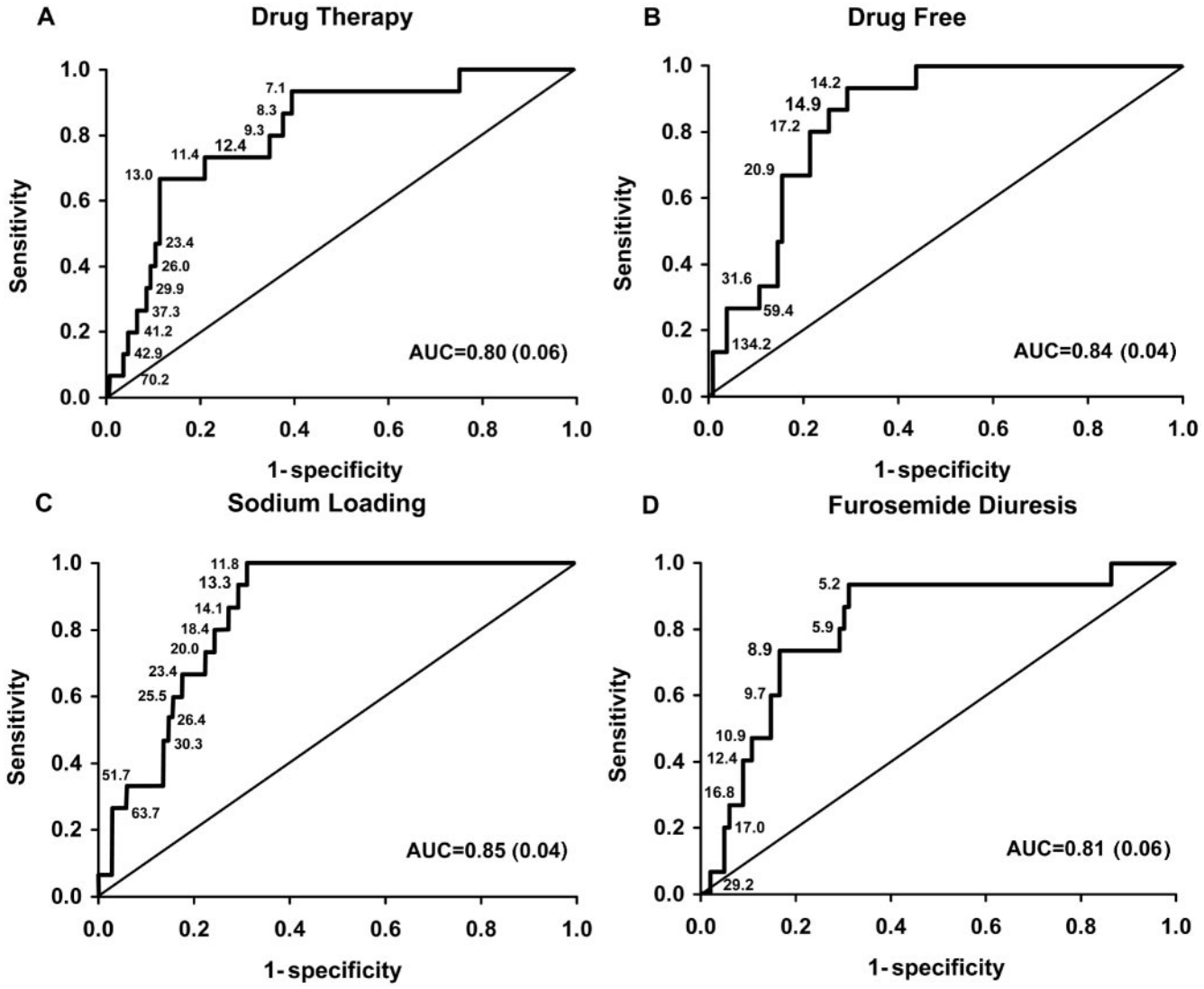

Fig. 2. ROC curves for the aldosterone:PRA ratio determined under the clinical conditions of concurrent antihypertensive drug therapy (*A*), after a minimum 2-week antihypertensive-drug-free interval (*B*), after 4 days of dietary sodium loading (*C*), and after acute furosemide diuresis (*D*).

Values of the ratio at various points on the curve are displayed in conventional units of mL/dL · h. *Bold values* represent the optimum value of the ratio under each clinical condition. *AUC*, area under the ROC curve.

participants were off antihypertensive drug therapy (Table 2). The 95% CIs for these point estimates are shown in Table 2.

The diagnostic sensitivity of the optimum ratio value was highest when measured after dietary sodium loading (93%) and lowest when measured either when partici-

Table 2. Test characteristics of the aldosterone:PRA ratio to screen for primary aldosteronism.

	Drug therapy	Drug free	Sodium loading	Acute diuresis
Optimum ratio (95% CI), mL/dL · h	12.4 (7.1–16.6)	14.9 (14.2–20.9)	13.3 (11.8–25.5)	8.9 (5.2–9.7)
Sensitivity (95% CI), %	73 (50–96)	87 (70–100)	93 (80–100)	73 (50–96)
Specificity (95% CI), %	74 (65–83)	75 (66–84)	71 (62–80)	84 (77–91)
Likelihood ratio				
Positive test	2.8	3.4	3.2	4.4
Negative test	0.36	0.18	0.10	0.32
Predictive value, %				
Positive test	29	33	32	41
Negative test	95	97	99	96

pants were on antihypertensive drug therapy or after acute furosemide diuresis (73% under both conditions; Table 2). Sensitivity was intermediate when measured when participants were off antihypertensive drug therapy (87%). Specificity of the optimum ratio value was highest when measured after furosemide diuresis (84%) and lower when measured under the other clinical conditions (71–75%). The 95% CIs for the point estimates of sensitivity and specificity are shown in Table 2.

For optimum values of the aldosterone:PRA ratio (Table 2), the likelihood ratio for a positive test was highest after acute furosemide diuresis (4.4) and lowest when measured when participants were on antihypertensive drug therapy (2.8). The likelihood ratio for a negative test was lowest for the aldosterone:PRA ratio measured after dietary sodium loading (0.10) and highest when measured when participants were on antihypertensive drug therapy (0.36).

LIKELIHOOD RATIOS ASSOCIATED WITH RANGES OF ALDOSTERONE:PRA RATIO VALUES

Because the overall diagnostic accuracy of the ratio did not differ significantly across clinical conditions, likelihood ratios associated with increasing ranges of values of the aldosterone:PRA ratio are shown only for the two clinical conditions most likely to be used in clinical practice, i.e., on or off antihypertensive drug therapy. Under either of these conditions, ratio values >15 mL/dL · h were associated with 2.4- to 13-fold increases above the pretest odds for primary aldosteronism (Table 3).

Discussion

The results of our study demonstrate that measurement of the aldosterone:PRA ratio to screen for primary aldosteronism has only fair diagnostic accuracy that is not significantly affected by concurrent antihypertensive drug therapy or acute variation in dietary sodium balance. This implies that the ratio can be determined without the need for prior discontinuation of antihypertensive drug therapy or imposition of a controlled sodium diet. In general, values of the ratio >15 mL/dL · h were associated with an increase above the pretest odds for primary aldosteronism; however, ranges of values of the ratio and their associated likelihood ratios may be more clinically useful and informative than a single cutpoint value. The results of our study also demonstrate that primary aldosteronism, as currently defined, is common among adults with presumed essential hypertension.

Montori and Young *(14)* recently conducted a systematic review of prospective studies of the aldosterone:PRA ratio as a screening test for primary aldosteronism. The review included 16 studies with >3000 participants. They noted that none of these studies evaluated the ratio and the reference standard independently of each other; only two studies evaluated individuals who had a "negative" ratio with the reference standard; and only 16.7% of the participants had both the ratio and the reference standard performed. In these studies, cutpoint values of the ratio ranged from 7.2 to 100 mL/dL · h. Moreover, the origin of the study samples (primary care, referral, or hospitalized patients), the clinical conditions of measurement (usual vs low-salt diet; on or off antihypertensive drug therapy), and the details of measurement (time of day, body position, and specific methods used to measure PRA and aldosterone) all varied among studies. In most studies, the rationale for the chosen cutpoint value of the ratio was not explicitly disclosed. The authors of the review concluded that: "there are no published valid estimates of the test characteristics of the aldosterone:PRA ratio when used as a screening test for primary aldosteronism in patients with presumed essential hypertension." Our study overcomes most of these deficiencies and provides the first estimate of the diagnostic accuracy of the ratio when used to screen individuals from the community with presumed essential hypertension for primary aldosteronism, the group most commonly considered for this disorder.

Diagnostic sensitivities associated with optimum values of the ratio were only modest when measured when participants were either on or off antihypertensive drug therapy (73–87%). This is not unexpected because it is

Table 3. Effect of aldosterone:PRA ratio values on pretest odds of primary aldosteronism in the study sample when measured in patients on or off antihypertensive drug therapy.

	Pretest odds (probability)	Ratio value	Likelihood ratio	Posttest odds (probability)
On antihypertensive drug therapy	0.15 (13%)	0–10	0.39	0.06 (6%)
		10–15	0.72	0.11 (10%)
		15–20	7.0	1.05 (51%)
		20–25	13.0	1.95 (66%)
		>25	3.6	0.54 (35%)
Off antihypertensive drug therapy	0.15 (13%)	0–10	0.12	0.02 (2%)
		10–15	0.41	0.06 (6%)
		15–20	2.9	0.44 (30%)
		20–25	5.0	0.75 (43%)
		25–30	13.0	1.95 (66%)
		>30	2.4	0.36 (26%)

known that the ratio can vary greatly and that "normal" values are not uncommon in individuals with primary aldosteronism. For example, in a recent study of repeated measures of the ratio under random and standardized conditions in 71 patients with confirmed primary aldosteronism attributable to aldosterone-producing adenomas *(24)*, normal ratio values were observed in 31% of patients on at least one occasion and in only 37% of patients was the ratio increased on all occasions of measurement. These observations support the possibility that modest further increases in sensitivity might be achieved by obtaining repeated measures of the ratio, as suggested by Gordon *(9)*. However, the benefit of this approach would have to be balanced against its associated added cost and inconvenience.

Specificities associated with optimum values of the ratio were also only modest when measured when participants were either on or off antihypertensive drug therapy (74–75%). One explanation for the relatively low specificity is the frequency of low PRA in hypertensive patients *(9, 25)*. As we have previously pointed out, most of the variation in the ratio in patients with essential hypertension is attributable to variation in PRA, and in many patients, an increased ratio is simply an indicator of low PRA *(26, 27)*. To improve the specificity of the ratio, some have advocated the addition of a threshold value of aldosterone as part of the screening criteria *(4, 13)*. Although such a strategy increases the specificity of the test (i.e., decreases the number of false positives), it also markedly decreases sensitivity (i.e., increases the number of false negatives). For example, imposition of a threshold value of aldosterone of >15 ng/dL, as suggested by the authors in the above-cited studies, to the optimum ratio of >12.4 mL/dL · h (when screening individuals on antihypertensive drug therapy) increased the specificity in our sample from 74% to 97% but markedly decreased the sensitivity from 73% to 33%. Thus, based on our findings, such a strategy is ill advised in screening for primary aldosteronism.

Differences in clinical conditions at the time of screening that influence PRA and aldosterone may also influence the test characteristics of the ratio. A common and important clinical condition is concomitant antihypertensive drug therapy. In a sample of 154 adults with known primary aldosteronism, Mulatero et al. *(15)* reported that a beta-blocker (atenolol) increased the mean ratio by 62%, whereas, a calcium antagonist (amlodipine), an angiotensin-converting enzyme inhibitor (fosinopril), and an angiotensin II receptor blocker (irbesartan) decreased the mean ratio by 17%, 30%, and 43%, respectively. In a previous study, we found that a thiazide diuretic (hydrochlorothiazide) decreased the mean ratio by 36% *(26)*. Although these studies clearly demonstrate that antihypertensive drugs may influence ratio values, this is the first study to assess the overall effects of the presence of antihypertensive drug therapy on the diagnostic accuracy of the ratio. As expected, the presence or absence of antihypertensive drug therapy influenced optimum cutoff values of the ratio, e.g., 12.4 mL/dL · h on drug therapy vs 14.9 mL/dL · h off drug therapy; however, the diagnostic accuracy of the test defined by the area under the ROC curves was not significantly affected [0.80 (0.06) vs 0.84 (0.04); $P = 0.49$]. Discontinuation of antihypertensive drug therapy before screening is time-consuming and potentially dangerous, and our results suggest that it is not necessary.

Another clinical condition at the time of screening that could influence the test characteristics of the ratio is dietary sodium balance. Clearly, dietary sodium restriction is associated with increases in both PRA and aldosterone concentration, whereas dietary sodium loading is associated with opposite effects. However, the influence of these changes on the ratio has not been systematically investigated. In our study, similar to the observed effects of the presence or absence of antihypertensive drug therapy, acute changes in dietary sodium balance influenced the optimum cutpoint value of the ratio (e.g., 13.3 mL/dL · h after sodium loading vs 8.9 mL/dL · h after acute diuresis), but did not significantly affect the diagnostic accuracy of the test [area under the ROC curve, 0.85 (0.04) vs 0.81 (0.06); $P = 0.51$]. These results suggest that imposition of a controlled sodium diet before screening is also unnecessary.

A practical problem with application of the ratio in clinical practice is deciding on which of several published cutpoint values to use for a positive test *(14)*. The tradition of reporting a single cutpoint value for the ratio does not take full advantage of the information provided by any single value obtained during screening. In reality, useful information for clinical decision-making can be provided by any value of the ratio. Thus, we display in Table 3 the likelihood ratios associated with ranges of values of the ratio that could be used by the clinician to determine the impact of any measured value on the probability of disease. In general, higher ranges of ratio values were associated with correspondingly higher likelihood ratios; however, this was not the case for the highest ranges (>25 mL/dL · h on drug therapy and >30 mL/dL · h off drug therapy). This is likely a consequence of the small number of individuals in our sample with ratio values in these highest ranges.

Our study, consistent with several recent reports, indicates that primary aldosteronism is common in patients with presumed essential hypertension *(1–8)*. In these recent series, idiopathic hyperaldosteronism attributable to presumed bilateral adrenal hyperplasia was the most common subtype, accounting for two thirds of cases, with a unilateral adrenal cortical adenoma accounting for the remainder *(8)*. All of the participants in our study who met the diagnostic criteria for primary aldosteronism underwent high-resolution computed tomography imaging of the adrenal glands, and none was found to have an adenoma. In part, this may reflect the study sampling method, which excluded adults with severe hypertension

or unexplained hypokalemia, among whom adrenal cortical adenoma is more common. Controversy exists as to whether idiopathic hyperaldosteronism represents a state of true autonomous overproduction of aldosterone, as is observed in adrenal cortical adenoma, or if it should be more properly considered a form of low-renin essential hypertension *(28–30)*.

This study has several limitations. Because we restricted sampling to adults with only mild to moderate hypertension who did not have unexplained hypokalemia, application of the ratio test characteristics determined in this study to patients referred for severe hypertension or unexplained hypokalemia is uncertain. However, we believe that the participants in this study are representative of patients encountered in a primary care practice, a setting where use of the ratio has been advocated *(8, 9)*. Because of the small sample size, we could not assess the impact of any specific drug class on the test characteristics of the ratio. Although we did not demonstrate an overall effect of antihypertensive drug therapy on test characteristics of the ratio, it is still possible that the effects of specific drug classes could be substantial. In addition, none of the patients in our study were taking aldosterone-receptor-blocking drugs, which are assumed to impact the test characteristics of the ratio *(9, 13)*. Finally, the test characteristics of the ratio determined in this study may not apply if sampling conditions (blood samples obtained after 5 min in the seated position at 0800) or the specific laboratory methods used to measure PRA and aldosterone are not the same as those used in this study.

In conclusion, the results of this study demonstrate that primary aldosteronism is common among adults in the community with presumed essential hypertension. Although determining the aldosterone:PRA ratio is simple and relatively inexpensive, the ratio has only fair diagnostic accuracy in screening for this disorder. Whether widespread screening for primary aldosteronism is appropriate awaits the results of future studies to determine the practical impact of making this diagnosis on the management and control of hypertension. If it is found that widespread screening for primary aldosteronism is appropriate, test reporting of likelihood ratios associated with ranges of ratio values may be more useful than consideration of a single optimum value.

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