MAYO CLINIC LABORATORIES

Renin-Aldosterone Studies

A. Renin-Angiotensin-Aldosterone System

Renin is secreted by the juxtaglomerular cells of the kidneys in response to changes in plasma volume. An increase in renin normally produces an increase in aldosterone through angiotensin intermediates. Renin's physiological effects are manifested mainly through its regulation of aldosterone production. Aldosterone is produced by the adrenal cortex and normally fluctuates in response to changes in renin levels. With aldosterone-producing tumors, the serum aldosterone level is elevated even though renin is suppressed. Aldosterone production results in retention of sodium and excretion of potassium.

B. Usual Laboratory Test Findings in Renin-Aldosterone Disorders

1. Renal disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal vein catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) greater than 1.5.
2. Primary aldosteronism is common, affecting approximately 5% to 14% of patients with hypertension. It is manifested by low renin and elevated aldosterone levels. In individuals with primary aldosteronism, the aldosterone level will not be suppressed by a high sodium intake, whereas in normal individuals it will. Patients with primary aldosteronism will have suppressed plasma renin activity (≤ 1 ng/mL/h) and inappropriately high aldosterone (≥ 7.5 ng/dL, when measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The aldosterone-to-renin ratio in patients with primary aldosteronism is typically ≥ 15. An elevated urinary aldosterone excretion rate and increased levels of serum aldosterone associated with low plasma renin activity is presumptive evidence for primary aldosteronism. Primary aldosteronism exists on a continuum of autonomous aldosterone excess and is more prevalent than previously recognized. Any patient with hypertension should be screened for primary aldosteronism.

C. Preparation of Patient for Plasma Renin Activity (PRA) Determination

1. When screening for primary aldosteronism, no preparation is required. However, it is recommended for testing to be done in the morning, in a seated position, avoiding sodium restriction before testing, and hypokalemia corrected with potassium supplements. Medication withdrawal is not usually required to perform screening for primary aldosteronism. It may be difficult to interpret data obtained from patients treated with a mineralocorticoid receptor antagonist (spironolactone and eplerenone). These drugs prevent aldosterone from activating the receptor, resulting sequentially in sodium loss, a decrease in plasma volume, and an elevation in plasma renin activity (PRA), which will reduce the utility of the aldosterone-to-PRA ratio. For this reason, spironolactone and eplerenone should not be initiated until the evaluation is completed and the final decisions about treatment are made. However, there are exceptions to this rule. For example, if the patient is hypokalemic despite treatment with spironolactone or eplerenone, then the mineralocorticoid receptors are not fully blocked and PRA should be suppressed in such a patient with primary aldosteronism. In addition, most patients with primary aldosteronism who are treated with mineralocorticoid receptor antagonists are given sub-therapeutic dosages. In this unique circumstance, the evaluation for primary aldosteronism can proceed despite treatment with mineralocorticoid receptor antagonists. Thus, plasma aldosterone concentration and PRA should be measured in patients treated with spironolactone or eplerenone. If PRA is suppressed, these medications are not interfering and therefore, case detection testing, confirmatory testing, and adrenal venous sampling can be performed without discontinuing the mineralocorticoid receptor antagonists. However, if PRA is not suppressed, then the mineralocorticoid receptor antagonist therapy should be discontinued for at least 4 to 6 weeks before re-testing. Other potassium-sparing diuretics, such as amiloride and triamterene, usually do not interfere with testing unless the patient is on high doses.
2. When performing renal vein renins to investigate renovascular hypertension, the angiotensin converting enzyme (ACE) inhibition protocol may be used.

   It has been shown that acute administration of drugs that block the action of ACE will enhance renin lateralization. Surprisingly, the effect is not seen if these drugs are given chronically. An advantage of this protocol is that the inhibiting effects of other drugs can be eliminated, and it is unnecessary to allow a washout period to pass. Typical ACE-inhibitors include captopril, enalapril, and lisinopril.

   Administer captopril 25 mg by mouth 30 minutes prior to the procedure. Caution should be taken to guard against orthostatic hypotension.

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D. Preparation of Patient and Specimens for Primary Aldosteronism Study

1. Case detection testing—the serum aldosterone to plasma renin activity (SA/PRA) ratio
   a. No salt depletion is necessary.
   b. Collect a simultaneous blood specimen for serum aldosterone and plasma renin activity before 10 am. No special posture instructions are needed. Blood should be drawn in the seated position. The SA/PRA ratio may be performed while the patient is on antihypertensive medications. Spironolactone and eplerenone are the only medications that may interfere with interpretation of the ratio. ACE inhibitors and angiotensin receptor blockers (ARBs) have the potential to "falsely elevate" PRA. Therefore, in a patient treated with an ACE inhibitor or an ARB, the findings of a detectable PRA level or a low SA/PRA ratio do not exclude the diagnosis of primary aldosteronism. In addition, a strong predictor for primary aldosteronism is a PRA level undetectably low in a patient taking an ACE inhibitor or ARB.
   c. A high ratio of SA (in ng/dL) to PRA (in ng/mL/hour) is a positive screening test result, a finding that warrants further testing. In the setting of suppressed renin, SA ≥ 10 ng/dL indicates primary aldosteronism, and even lower SA levels of 6 to 10 may indicate primary aldosteronism.
2. Confirmatory testing—aldosterone suppression testing
   Confirmatory testing may be omitted when the patient presents with resistant hypertension, spontaneous hypokalemia, undetectable renin and clear elevation of aldosterone (ie, > 20 ng/dL), familial hyperaldosteronism, or when a patient will be treated with medications (not undergoing subtyping with adrenal vein sampling). The list of drugs and hormones capable of affecting the renin-angiotensin-aldosterone axis is extensive. Frequently, in patients with severe hypertension, a "medication-contaminated" evaluation is unavoidable. Calcium channel blockers and alpha1-adrenergic receptor blockers do not affect the diagnostic accuracy in most cases. It may be impossible to interpret data obtained from patients receiving treatment with spironolactone or eplerenone (see above).

Aldosterone suppression testing can be performed with orally administered sodium chloride and measurement of urinary aldosterone or with intravenous sodium chloride loading and measurement of SA. Our practice has been oral salt loading over 3 days. After hypertension and hypokalemia are controlled, patients should receive a high sodium diet (supplemented with sodium chloride tablets if needed) for 3 days. The risk of increasing dietary sodium in patients with severe hypertension must be assessed in each case. Because the high sodium diet can increase kaliuresis and hypokalemia, vigorous replacement of potassium chloride may be needed. On the third day of the high sodium diet, a 24-hour urine specimen is collected for measurement of aldosterone, sodium, and creatinine. The 24-hour urinary sodium excretion should exceed 200 mEq to document adequate sodium repletion. Urinary aldosterone excretion greater than 12 mcg/24 hours in this setting is consistent with hyperaldosteronism.

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