Diagnosis of Secondary Forms of Hypertension

A Comprehensive Protocol

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- An efficient protocol for the evaluation of hypertensive cases included renal arteriography, suppression and stimulation of the renin-aldosterone system, and, when indicated, renal venous renin measurements. It permitted identification of 38 patients with renal artery stenosis, 28 with primary aldosteronism, and 51 with high renin, 92 with normal renin, and 27 with low renin essential hypertension.

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PHYSICIANS frequently encounter hypertensive cases for which a comprehensive evaluation is desired. Reasons for further study may include inadequate blood pressure control, young age of the patient, sudden or recent onset of hypertension, or the suspicion of a secondary form of hypertension. In addition, renin "profiling" of hypertensive patients has frequently been used by practitioners as the basis for specific antihypertensive therapy. The widespread availability of diagnostic procedures, such as renal arteriography and radioimmunoassay measurements of the renin-angiotensin-aldosterone system, makes it possible for such evaluation to be performed at most community hospitals.

This communication describes an efficient way to examine the hypertensive patient for the most common forms of remediable hypertension—renal artery stenosis and primary aldosteronism—in a referral center. We believe this approach may be used by physicians in their own practice when they deem it necessary. An additional benefit of this approach is the ability to classify hypertensive patients on the basis of the dynamic responses of the renin-angiotensin-aldosterone system to suppressive and stimulatory maneuvers. We studied 236 hypertensive subjects, including 38 with renal vascular hypertension and 28 with primary aldosteronism as well as 114 normotensive subjects who served as controls for the biochemical measurements.

METHODS

Patients

Patient Selection.—To define normal values for the humoral studies, observations were made in 114 normal volunteers—47 white men, 43 white women, 14 black men, and 10 black women—who ranged in age from 14 to 72 years. The subjects were hospitalized at the Indiana University Clinical Research Center. The protocol was approved by the Indiana University Medical Center Human Use Committee, and informed consent was obtained.

Hypertensive Patients.—In the period of Jan 1, 1974, to Jan 1, 1976, 236 hypertensive patients were referred to our institution for evaluation by their primary care physicians and were judged to be candidates for the protocol to be described. Patients who were not thought to be surgical candidates were excluded from this study: papilledema, retinal hemorrhages, congestive heart failure or history of such in the preceding three months, peripheral edema, angina pectoris, history of myocardial infarction, cerebral vascular accident within the preceding three months, or a history of a transient ischemic attack.

Since estrogens are known to interfere with measurements of the renin-angiotensin-aldosterone system as well as influence blood pressure, patients receiving birth control pills or estrogen therapy were not studied until three months after cessation of such medication. Before admission, treatment with all antihypertensive agents was discontinued for 14 days. Patients who had been taking spironolactone (Aldactone) for less than one month prior to admission were also excluded because this drug may occasionally cause long-term elevation of renin levels. Dietary sodium and potassium intake were unrestricted before admission; on admission, dietary sodium intake was 150 mEq/day and potassium, 70 mEq/day. Hypertensive patients generally had rapid sequence intravenous urography prior to hospital admission, and renal arteriography was scheduled in advance for the day after admission to the
Algorithm for evaluation of secondary hypertension. Asterisk indicates that normal values provided are specified for our laboratory techniques; when different techniques are used or provided by another laboratory, normative data need to be obtained.
hospital. The algorithm (Figure) provides a flow diagram for the following detailed hypertensive evaluation.

Protocol for Study

Day 1. Admission.—On this day the patients were admitted to the hospital and acquainted by the ward personnel with the procedures to be performed.

Day 2. Arteriogram.—When not contraindicated, a transfemoral renal arteriogram with selective renal artery studies was performed to identify renal vascular lesions. If the angiogram was abnormal, the patient was scheduled for differential renal venous renin sampling on day 5. Normal subjects or hypertensive patients not judged to be operative candidates did not undergo this procedure.

Day 3. Saline Infusion.—To evaluate the suppressibility of the renin-angiotensinaldosterone system, the patient was awakened at 6 AM and was asked to assume the upright posture (standing or walking) until 8 AM, at which time blood samples were obtained for measurements of plasma renin activity (PRA) and plasma aldosterone (PA). The patient was supine from 8 AM until noon while receiving an intravenous infusion of 2 liters of normal (0.9%) saline (500 ml/hr) beginning at 8 AM. At noon, blood was again obtained for PRA and PA. Food was withheld until after the noon blood samples had been obtained. The total sodium intake on this day was 458 mEq. The 24-hour urine collected on this day was analyzed for creatinine and catecholamine content.

Day 4. Furosemide.—Sodium and volume depletion was induced to stimulate renin. At 8 AM, after two hours of upright posture but before sodium and volume depletion was initiated, blood was again obtained for PRA. The diet on this day was limited to 10 mEq sodium, 70 mEq potassium, and 25 ml/kg body weight of free diet fluid. Furosemide (Lasix) was given orally (40 mg) at 9 AM, 1 PM, and 5 PM.

Day 5. Post-sodium Depletion.—To evaluate the response of PRA to the stimulus of upright posture following sodium and volume depletion induced on the previous day, blood was again sampled for PRA at 8 AM, after two hours of upright posture. Some patients were not able to walk for the full two hours on this morning, and in those instances the sample was collected when the patient felt faint. If the renal arteriogram was abnormal on day 2, renal venous renin samples were collected while the patient was recumbent and after a 45° tilt for 20 minutes on this day.

Twenty-four-hour urine collections were obtained on each of the study and analyzed for volume, sodium, potassium, and creatinine content. Serum was obtained for measurements of electrolyte and creatinine content and calculation of endogenous creatinine clearance.

Laboratory Methods

Sodium, potassium, and creatinine concentrations in blood and urine were measured by autoanalyzer. Plasma renin activity and plasma aldosterone were measured by radioimmunoassay. Urinary catecholamine excretion was measured by a fluorometric method. Statistical analyses were performed with the use of parametric or nonparametric techniques as appropriate.

RESULTS

Normal Subjects

The age of the normal subjects was 32±14 years (SD); the range was 14 to 77 years. Table 1 indicates observations of serum and urinary electrolytes and body weight in normal subjects during the study. Table 2 indicates mean values ±1 SD for PRA and PA levels at 8 AM before saline and at noon after saline administration, and it shows the observations for plasma renin activity alone at 8 AM before and after furosemide administration. In 95% of this normal population, the PRA level was less than 12.0 ng/ml/3 hr before saline infusion and less than 2.6 ng/ml/3 hr after. In 95% of the normal population, the PA level was less than 65.0 ng/100 ml before saline infusion and less than 11.0 ng/100 ml after. On the next morning, 95% of the normal subjects had a PRA level less than 10.0 ng/ml/3 hr. The morning following the volume and sodium depletion maneuver, the PRA level was greater than 3.9 ng/ml/3 hr in 95% of the normal population.

Hypertensive Subjects

Renal Vascular Hypertension.—Included in this group were 38 patients who had demonstrable renal arterial narrowing on renal arteriography and a renal venous renin ratio of 1.5:1 (involved to uninvolved) or greater. Eighteen of these patients had a blood pressure of less than 140/90 mm Hg with or without therapy at least six months after surgical intervention; the remaining 20 were either treated medically or had recently undergone surgery. Several patients in this group, for one or more of the reasons described, did not have all of the protocol studies.

Of the 18 patients with proved renal vascular hypertension, a systolic and diastolic epigastric bruit was detected in ten (56%); an abnormal intravenous pyelogram (IVP), defined according to the criteria of the Cooperative Study, was present in 13 (72%); and both an epigastric bruit with a systolic and diastolic component and an abnormal IVP were present in 16 (89%).

Table 2 shows the renin-aldosterone results in these patients. At every point, mean PRA and PA levels were significantly (P<.05) higher than normal. Of the 18 patients with surgically proved renal vascular hypertension, 14 (78%) had peripheral plasma renin activity after two hours of ambulation during an unrestricted sodium intake, which was above the 95% confidence limits for the normal population. An abnormal IVP, continuous abdominal bruit, or a "before saline" PRA level greater than 12 ng/ml/3 hr was observed in 17 of these 18 patients (94%).

Primary Aldosteronism.—Included in this group were 28 patients in whom the diagnosis of primary aldosteronism was confirmed at the time of sur-
**Table 2.—Mean Observations in Normal and Hypertensive Subjects**

<table>
<thead>
<tr>
<th>Blood Pressure, mm Hg</th>
<th>PRA, ng/ml/3 hr</th>
<th>PA, ng/100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Normal subjects (n=114)</td>
<td>33</td>
<td>114</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Renovascular hypertension (n=38)</td>
<td>45</td>
<td>187</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>Primary aldosteronism (n=28)</td>
<td>48</td>
<td>180</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Essential hypertension (n=170)</td>
<td>42</td>
<td>187</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>Low renin (n=27)</td>
<td>49</td>
<td>170</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>Normal renin (n=92)</td>
<td>41</td>
<td>165</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>High renin (n=51)</td>
<td>40</td>
<td>172</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>13</td>
<td>30</td>
</tr>
</tbody>
</table>

*PRA indicates plasma renin activity; PA, plasma aldosterone.*

Surgery or in whom indeterminate aldosteronism was suspected and treatment with spironolactone controlled the blood pressure. All 28 patients demonstrated a failure of PA levels to be suppressed to less than 11 ng/100 ml after saline infusion and a failure of PRA levels to increase to 4 ng/ml/3 hrs or greater after furosemide administration.

Of the 14 patients with surgically proved adenoma, four (29%) had serum potassium levels of 3.5 mEq/liter or greater when first seen. In the 14 patients with indeterminate aldosteronism, seven (50%) had normal serum potassium levels.

Seven of 28 patients with hyperaldosteronism (25%) had normal PRA levels before saline infusion. Similar observations of PRA levels in these patients were made at the "after saline" and "before furosemide" sampling times. Levels of PA before the saline infusion were normal in 98% of these patients. Thus, in our experience the diagnosis of primary aldosteronism can best be made by demonstrating a failure of PA to be suppressed to normal levels with saline and PRA to be stimulated to normal levels with furosemide.

**Essential Hypertension.**—There were 170 hypertensive patients without evidence of renal artery stenosis, primary aldosteronism, excessive catecholamine production, coarctation of the aorta, or other identifiable secondary forms of hypertension. Renal arteriograms performed in 76 patients were normal. All patients had normal intravenous pyelograms, and none had a continuous epigastric bruit. They were thus considered to have "essential" hypertension. The mean values for PRA and PA are shown in Table 2.

When these patients were further subdivided (Table 2) on the basis of the comparative responses of PRA and PA to the normal confidence limits, 51 (30%) had high renin, characterized by a failure of PRA to be suppressed to levels of 2.6 ng/ml/3 hr or less following saline infusion. Twenty-seven patients (16%) had low renin essential hypertension characterized by failure of PRA to be stimulated to levels of 3.9 ng/ml/3 hr after furosemide administration, and 92 (54%) had normal renin essential hypertension with observations for PRA and PA that were consistently normal.

Arteriograms were performed in more than 100 hypertensive patients; only one major complication was observed—an inguinal hematoma from a lacerated femoral artery.

**COMMENT**

Our study indicates that a comprehensive evaluation of patients for secondary hypertension can be accomplished with the aid of the outlined protocol.

The only unequivocal method for identifying renal artery stenosis is by renal arteriography. In our experience, the IV pyelogram was interpreted as normal in 29% of patients with renal vascular hypertension. The most frequently abnormal PRA level in renal vascular hypertension was observed following the attempted suppression of renin. None of the patients in our study with surgically proved renal vascular hypertension had a subnormal renin level after stimulation by volume and sodium depletion. The final diagnosis of hypertension caused by unilateral artery stenosis requires renal venous renin measurement under stimulated conditions.

In primary aldosteronism, random or ambulatory peripheral PRA or PA levels were not useful in making the diagnosis, as many of those who subsequently proved at surgery to have this disorder had normal levels before saline infusion. Serum potassium
level was 3.5 mEq/liter or greater in one third of these patients.

The biochemical syndrome of primary aldosteronism does not always represent a patient with a unilateral adrenal tumor. The differentiation of unilateral and bilateral forms of hyperaldosteronism may require adrenal venography, adrenal vein sampling for aldosterone concentrations, and isotopic scanning of the adrenal gland. In our experience, the separation of unilateral and bilateral forms of primary aldosteronism is best made by the measurement of aldosterone in adrenal venous blood during adrenocorticotrophic hormone stimulation to eliminate errors from episodic production of steroids or dilution of adrenal effluent. Such sophisticated procedures may require the facilities of a referral center for completion, but the primary care physician can make the initial diagnosis on the basis of the observations outlined in the present protocol.

The dynamic responses of the renin-angiotensin-aldosterone system to saline infusion and furosemide-induced sodium and volume depletion with ambulation in the normal subjects suggests that this protocol is a useful way of rapidly inducing suppression and stimulation of this system. Subjects with "essential" hypertension in whom renal artery stenosis and primary aldosteronism were excluded can be separated into three groups on the basis of the adequacy of suppression of PRA with saline infusion and stimulation with the furosemide-induced sodium and volume depletion. It has been suggested that this classification of "essential" hypertensive patients may be a useful technique for deciding on specific antihypertensive therapy. This area of investigation is being pursued by several groups. The low-renin, essential hypertensive patients were separated from those with primary aldosteronism on the basis of a normal suppression of PRA levels following saline infusion in the former group.

The absolute values for PRA and PA reported in this study may not be applicable to all such measurements made in other laboratories since there are considerable variations in methodology.

In summary, we believe this comprehensive protocol will enable the practitioner to accurately diagnose the major secondary causes of hypertension in patients for whom he thinks such procedure is necessary.

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Hoon Yune, MD, Department of Radiology, performed the roentgenographic studies in the hypertensive subjects, and John Donohue, MD, Department of Urology, performed the surgical procedures in those patients undergoing renal vascular and adrenal surgery. Emily Roberts, RN, directed the studies on the Clinical Research Center. Technical assistance was provided by Mary Wade, Maria Ong, Jackie Broadley, Jennifer Eberts, Karen Evasion, and Thomas Winkler. Gwendolyn Morgan and Annette Russell helped in the preparation of this communication. The house officers and nursing personnel at Indiana University Medical Center helped conduct the hypertensive studies. Further details and preprinted hospital order sheets for the protocol for hypertensive patients are available from the authors on request.

References