Detection, Evaluation, and Treatment of Renovascular Hypertension

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Final Report

Working Group on Renovascular Hypertension

Careful interpretation of clinical clues continues to provide valuable information to identify patients in whom further evaluation for renovascular hypertension (RVH) is needed. Newer diagnostic techniques such as intravenous digital subtraction angiography and computer-generated renal flow scans have helped to more accurately identify patients in whom renal arteriography is indicated. More sensitive and specific tests are still needed to establish the hemodynamic significance of renal artery lesions. New classes of antihypertensive drugs, particularly B-blockers and angiotensin-converting enzyme inhibitors, have enabled the control of blood pressure in most patients with RVH but do not assure preservation of renal function. An aggressive search for and correction of coexisting risk factors, and improved surgical techniques, have resulted in lower surgical mortality. The development of percutaneous transluminal renal angioplasty has provided an invasive, nonsurgical method for managing RVH in selected patients.

(Arch Intern Med 1987; 147:820-829)

In the last decade, a number of important advances have improved the detection, evaluation, and treatment of renovascular hypertension. This article critically reviews screening studies useful in identifying this disorder, the recommended approaches for confirming the diagnosis, and the selection of subsequent therapeutic options.

PREVALENCE

Current estimates suggest that more than 60 million Americans have arterial hypertension (1). With the possible exception of oral contraceptive use and alcohol ingestion, renovascular disease is the most common cause of potentially remediable secondary hypertension. Most of the available data on the prevalence of renovascular hypertension comes from case studies generated by tertiary care medical centers (2-4), and incidence figures as high as 32% have been reported when only patients with severe or accelerated hypertension are considered (5).

Probability sampling of the general population estimates the prevalence of renovascular hypertension to be 0.13% in the United States (6), with a similarly low incidence in Sweden (7). In all categories of hypertension, the prevalence of renovascular hypertension is substantially lower in black than in white patients (8, 9). Available estimates suggest that less than 0.5% of the hypertensive population has renovascular hypertension. It must be remembered that renal artery stenosis occurs in normal individuals and may exist for periods of years without detection.

Table 1. — Clinical Clues Suggesting Renovascular Hypertension

| Systolic/diastolic epigastric, subcostal, or flank bruit |
| Accelerated or malignant hypertension |
| Unilateral small kidney discovered by any clinical study |
| Severe hypertension in child or young adult, or after age 50 years |
| Sudden development or worsening of hypertension at any age |
| Hypertension and unexplained impairment of renal function |
| Sudden worsening of renal function in hypertensive patient |
| Hypertension refractory to appropriate three-drug regimen |
| Impairment in renal function in response to angiotensin-converting enzyme inhibitor |
| Extensive occlusive disease in coronary, cerebral, and peripheral circulation |

THE CLINICAL SETTING

The Cooperative Study of Renovascular Hypertension provided the first and only multicenter effort to define clinical features or characteristics suggestive of renovascular hypertension (9). The onset of hypertension before age 30 years should suggest secondary hypertension in contrast with older persons in whom essential hypertension is more prevalent (10). The abrupt onset of hypertension at any age or worsening of previously well-controlled hypertension suggests renovascular hypertension. Clinical clues that may help identify patients at higher risk and in whom further evaluation is warranted are listed in Table 1.

Few studies are available to verify a relationship of family history to renovascular hypertension. In many patients with atherosclerotic disease, a family history is likely because both hypertension and other cardiovascular risk factors for atherosclerosis tend to aggregate in families. Recent reports have emphasized that 80% to 90% of patients with atherosclerotic renovascular hypertension have a history of cigarette smoking.

When a patient has severe or accelerated hypertension, particularly a compliant patient whose blood pressure is refractory to an appropriate regimen, a secondary and potentially remediable form of hypertension should be considered. Extracranial carotid artery occlusive disease, significant coronary artery disease, or other evidence of peripheral vascular disease in older patients with resistant hypertension (>150/100 mm Hg), despite an appropriate three-drug regimen, should suggest further evaluation for renovascular disease.
The physical examination can provide clues to the presence of renovascular hypertension. Severe angiosclerotic changes, hemorrhages, and exudates on funduscopic examination correlate well with the severity of hypertension and warrant further evaluation for renovascular disease (9, 11). In patients suspected of having such retinal vascular changes, fundus photographs can often show the presence of these changes as well as gradual clearing in response to therapy.

Abdominal and flank bruits commonly occur in patients with renovascular hypertension. A continuous (systolic-diastolic) abdominal bruit has an especially high correlation with renovascular hypertension and is a better predictor of renovascular hypertension than any other single finding (11, 12). Examination for an abdominal bruit is best accomplished in a quiet environment with the patient supine. Gradual pressure is applied to the bell of the stethoscope, which is placed in several areas in the upper abdomen. Bruits are more commonly detected high in the upper quadrants of the abdomen than over the flank. The intensity of a bruit may vary with the patient's systemic blood pressure and may disappear if the blood pressure is controlled with drug therapy or if the stenosis becomes severe enough to decrease blood flow to a point where sound can no longer be generated.

Routine laboratory examination may find hypokalemia, suggesting aldosterone overproduction. If the patient has a small kidney unilaterally, unexplained renal functional impairment, microscopic hematuria, or proteinuria, the physician should suspect renovascular hypertension.

PATHOLOGY

The histologic and anatomic character of renal artery lesions is important in predicting the natural history and clinical relevance of renovascular hypertension. The angiographic appearance and location of a lesion, as well as the severity of stenosis, enables the clinician to determine what studies are appropriate for defining the functional significance of the stenosis and to plan appropriate therapeutic alternatives.

Lesions of the renal arteries associated with hypertension can be divided into several categories. Fibromuscular dysplasias and atherosclerosis are the most common causes of significant renal artery stenosis seen in the United States. Other causes, while uncommon, include Takayasu's aortitis, congenital anomalies including arteriovenous malformations or fistulas, neurofibromatosis, extrinsic obstruction of the renal artery, congenital coarctation of the abdominal aorta, and a miscellaneous group of disorders including renal artery thrombosis, embolism, and radiation injury.

ATHEROSCLEROTIC LESIONS

Approximately two thirds of all renovascular lesions in adults are caused by atherosclerosis, which affects twice as many men as women. Atherosclerosis may be limited to the renal artery but is more commonly a manifestation of generalized atherosclerosis involving the abdominal aorta and the coronary, cerebral, and peripheral extremity vessels. Occurrence is enhanced by cigarette smoking, hyperlipidemia, and diabetes. Available data regarding the natural history of atherosclerotic lesions of the renal arteries suggest that progressive obstruction is common, occurring in 40% to 45% of patients, and progression to total occlusion may occur in a significant number of patients (13, 14). The risk of progression to complete occlusion is highest in those patients with greater than 75% stenosis on initial angiography (Fig 1, left).

Bilateral atherosclerotic lesions are common and, in patients with an atrophic kidney, unsuspected stenosis may be present in the contralateral, normal-sized kidney. Atherosclerotic lesions may be complicated by medial dissection and subintimal hemorrhage, calcification, or atheromatosus embolus (15, 16).

On roentgenograms, the lesions usually involve the orifice and the proximal 2 cm of the renal artery, are usually eccentric, and may be complicated by poststenotic dilatation. If thrombosis or dissection have occurred with total occlusion, only a short stub of the renal artery may be evident. In approximately 15% to 20% of patients with atherosclerotic renal artery stenosis, lesions may not be associated with significant atherosclerotic disease elsewhere (Fig 1, right).

**FIBROMUSCULAR DYSPLASIA OF THE RENAL ARTERIES**

A clear understanding of the fibromuscular dysplasias, particularly the correlation of histopathologic and angiographic features, has been hampered by a lack of uniform terminology in many articles. We will use a unifying classification in this article (16, 17). Table 2 lists the recommended terms and the more common synonyms used in various articles. The fibromuscular dysplasias are classified based on the layer of arterial wall involved. The cause of these lesions is unclear, and they occur more commonly in women than in men.

Medial fibroplasia with or without mural aneurysms is the most common (60% to 85%) of the fibromuscular lesions and is usually seen as a multifocal "string-of-beads" lesion commencing in the midrenal artery with frequent extension into peripheral branches (Fig 2, left). Medial fibroplasia is typically seen in young to middle-aged women, may be bilateral, and has, occasionally, been demonstrated in celiac or carotid arteries. Although serial angiographic evaluations demonstrate that these lesions progress over time in approximately 33% of arteries observed, thrombosis or hemorrhagic dissection are rare, and the risk of total arterial occlusion is small.

Perimedial fibroplasia is the second most common variety (10% to 25%) of the fibromuscular dysplasias. The resulting irregular, severely stenotic lesion often has a beaded appearance angiographically, but the beads are smaller than the diameter of the unstenotic renal artery (Fig 2, right). Mural aneurysms may occasionally be associated with this lesion as well. The frequent observation of well-developed collateral blood vessels speaks to the severity of stenosis seen with this lesion.

Intimal fibroplasia may be seen in children as well as adults. This lesion is not confined to the main renal artery. It is usually seen as a sharply defined, highly occlusive stenosis and may represent, in some instances, a nonspecific, local response to injury. Medial hyperplasia is

<table>
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<th>Table 2.</th>
<th>Classification of Fibromuscular Dysplasia</th>
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<tr>
<td><strong>Recommended Classification</strong></td>
<td><strong>Synonyms</strong></td>
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<tr>
<td>Intimal fibroplasia</td>
<td>Intimal stenosis</td>
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<tr>
<td>Medial fibroplasia</td>
<td>Fibromuscular dysplasia; fibromuscular hyperplasia</td>
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<td>Medial hyperplasia</td>
<td>Fibromuscular dysplasia; fibromuscular hyperplasia</td>
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<tr>
<td>Perimedial fibroplasia</td>
<td>Fibromuscular dysplasia; perimedial fibroplasia; subadventitial fibroplasia; medidial hyperplasia</td>
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<tr>
<td>Periarterial fibroplasia</td>
<td>Subadventitial fibroplasia; periarterial fibrous stenosis</td>
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produced by hyperplasia of arterial smooth muscle without medial disruption or aneurysm formation and appears as a concentric, segmental stenosis. Periarterial fibroplasia, the least common of the fibrous lesions, consists of dense collagen that replaces the adventitia and extends into the periarterial fibrofatty tissues. Other arterial layers, including the external elastic membrane, are generally intact, and the lesion often has the angiographic appearance of a segmental, tubular, or irregular stenosis. Each of the above-mentioned lesions may be associated with medial dissection occurring in the outer zone of the media. In some cases, the underlying lumen may be obliterated, and the typical angiographic features of the original lesion may be lost.

Neurofibromatosis may be noted in children with renovascular hypertension. The importance of an aggressive search for secondary hypertension in children who have had a recent onset of moderate to severe hypertension cannot be overemphasized. It is also important to recognize that the histopathology of renal artery disease in children may be quite different from that observed in adults (18). Concentric or eccentric proximal (ostial) stenoses are seen in nearly 50% of patients and are often associated with neurofibromatosis or abdominal aortic coarctation or hypoplasia. Renal artery lesions, appearing as focal or long tubular stenoses, or as isolated segmental disease, comprise most of the remaining lesions observed in the pediatric population with renovascular hypertension. Many of these lesions appear to have a developmental origin.

Pathophysiology: The Renin-Angiotensin-Aldosterone System

The pathogenesis of renovascular hypertension has been the subject of extensive animal experimentation in an attempt to understand the physiologic and hemodynamic changes that occur in this condition in humans. The classic observations by Golblatt et al (19) in 1934 provided the first experimental models for renovascular hypertension.

Reduced renal perfusion causes release of renin and increases plasma angiotensin II levels with resultant vasoconstriction and systemic hypertension (20, 21). The relationship between elevated angiotensin II levels and increased blood pressure has been confirmed by the blood pressure lowering effects of angiotensin II antagonists and angiotensin-converting enzyme (ACE) inhibitors. Stimulation of aldosterone secretion by angiotensin II results in water and sodium accumulation with increases in extra-cellular fluid volume, which may help sustain blood pressure and lead to secondary suppression of renin. During this transition phase, hypertension still responds to angiotensin II antagonists or ACE inhibitors, or removal of the stenosis or the stenotic kidney. The effects of aldosterone and induced changes in intrarenal hemodynamics are important in the transition from an acute (early) phase to the chronic (late) phase of renovascular hypertension. The chronic phase of renovascular hypertension probably results from recruitment of multiple pressor mechanisms, which may be activated simultaneously or sequentially to sustain hypertension. Proposed mechanisms include increased vascular sensitivity to angiotensin II, vasoconstrictor and anti-diuretic effects of vasopressin, and impaired sodium transport by a ouabain-like natriuretic factor. Both the peripheral and central sympathetic nervous systems help maintain renovascular hypertension, as do structural changes in systemic blood vessels.

SCREENING AND DIAGNOSTIC STUDIES

There is disagreement on the sensitivity, specificity, and predictive value of various screening and diagnostic studies. The radionuclide, roentgenographic, and pharmacologic tests discussed here show the disparity in renal function caused by significant renal artery stenosis. The value of screening studies for renovascular disease can be significantly heightened by paying careful attention to clinical clues during the initial evaluation. Screening and diagnostic tests cannot, however, necessarily predict the success or failure of subsequent surgical intervention.

Rapid-Sequence Intravenous Urogram

This type of urogram is no longer performed routinely to assess patients with suspected renovascular hypertension (22). Although some studies have reported the urogram to be abnormal in up to 80% of patients with hemodynamically significant renovascular disease (23, 24), the high incidence of bilateral disease or segmental involvement seen in most medical centers today has significantly limited the sensitivity of this procedure. False-positive results may be seen in up to 12% of patients with essential hypertension. In patients with a history or laboratory findings suggesting renal parenchymal disease, obstructive uropathy, or calculous disease, urography continues to provide important diagnostic and therapeutic information.
Fig 2. — Left, Medial fibroplasia with mural aneurysms. Most common of the fibromuscular dysplasias, this beaded lesion begins in the mid renal artery and extends distally. In some cases, it may involve major branches and frequently occurs bilaterally. Right, Perimedial fibroplasia. This aggressive lesion, associated with high-grade stenosis, may have a beaded appearance but is not an aneurysmal lesion. Note early development of collateral circulation (arrows).

Nuclear Imaging Techniques
Safe, noninvasive, and relatively inexpensive isotope renography has proved less accurate than hypertensive urography in screening for renovascular disease, largely because of an unacceptable frequency of abnormal results in patients with essential hypertension. Radionuclide imaging techniques can provide information regarding both renal blood flow and excretory function, and renal perfusion-excretion ratios may increase the predictive value of radionuclide screening for renovascular hypertension (25). Assessing of transit times by this method has proved to be an important advance in the use of renography for diagnosing renovascular hypertension. The most appropriate contemporary use of renography is for longitudinal assessment of total and individual renal blood flow, particularly for patients with impaired renal function who are at increased risk from contrast media. More sophisticated computer programs and the increased ability to assess individual kidney function may further improve the value of isotope renography in assessing renovascular hypertension. Renographic changes after captopril administration may prove useful in demonstrating functional renal artery stenosis before, or after, surgical or catheter intervention.

Plasma Renin Activity
The casual measurement of plasma renin activity is of little value as a screening test or as a diagnostic test for renovascular hypertension in patients with renal artery stenosis (23). Accuracy can be improved if renin activity is indexed to urinary sodium excretion, especially when sodium intake and drug regimens can be carefully controlled. Unfortunately, attaining these rigid requirements is not practical in most clinical settings. Table 3 lists drugs and conditions that may stimulate or suppress plasma renin activity.

Digital Subtraction Angiography (DSA)
Digital subtraction angiography is a technique of imaging blood vessels whereby the background bone and the soft tissues of the body are subtracted from images made with iodinated contrast medium in the blood vessels. The final images show only the contrast medium outlining the lumen of the blood vessels. Intravenous DSA is less invasive than a direct arterial puncture, but the required dosage of contrast medium is higher, visualization of the main renal artery does not compare with that of standard arteriography, and renal arterial branches are seldom adequately visualized.

Intra-arterial DSA uses smaller volumes of contrast medium than conventional catheter arteriography, and it visualizes the renal arteries just as well. Some groups have combined digital subtraction angiography with renal vein renin sampling in an attempt to better identify patients with hemodynamically significant renal artery stenosis.

Arteriography
Catheter arteriography remains the “gold standard” in the diagnosis of renal artery stenosis. In the majority of patients, a single frontal aortogram is sufficient for adequate evaluation of the aorta, main renal arteries, and their proximal branches. The invasiveness and cost of arteriography make it an inappropriate screening test for
re renovascular hypertension. However, in selected patients where clinical evaluation strongly suggests the presence of renal artery stenosis, many clinicians will bypass other, less invasive screening studies and proceed directly to the arteriogram. In most cases, oblique or lateral views are also necessary to better visualize the origin of the renal arteries as well as the origin of the celiac axis, and selective arteriograms will help identify peripherally located branch lesions.

Injecting vasodilators or vasoconstrictors (pharmacologic angiography) into the renal circulation may enable visualization of collateral blood vessels not otherwise evident, which may also suggest a hemodynamically significant stenosis. Selective renal vein renin studies during angiography may allow the hemodynamic significance of lesions to be determined. Some angiographers today are prepared to perform transluminal angioplasty during aortography if a high-grade stenosis is identified.

### Table 3. Factors Affecting Renin Release

<table>
<thead>
<tr>
<th>Stimulatory</th>
<th>Inhibiting</th>
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<tr>
<td>Reduced renal blood flow</td>
<td>Decreased renal tissue</td>
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<tr>
<td>Renal artery stenosis</td>
<td>Volume expansion</td>
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<tr>
<td>Volume depletion</td>
<td>Adrenergic inhibition</td>
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<tr>
<td>Salt restriction</td>
<td>β-Adrenergic antagonists (β-blockers)</td>
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<tr>
<td>Blood loss</td>
<td>α-Adrenergic blockers (α-blockers)</td>
</tr>
<tr>
<td>Gastrointestinal tract losses</td>
<td>Disease conditions</td>
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<tr>
<td>Adrenergic stimulation</td>
<td>Hypertensive (primary)</td>
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<tr>
<td>Exercise</td>
<td>Diabetes mellitus</td>
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<tr>
<td>Upright posture</td>
<td>Hormones</td>
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<tr>
<td>Pharmacologic (vasodilation)</td>
<td>Aldosterone</td>
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<tr>
<td>Disease conditions</td>
<td>Vasopressin</td>
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<tr>
<td>Nephrotic syndrome</td>
<td>Hyperkalemia</td>
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<tr>
<td>Congestive heart failure</td>
<td>Drugs</td>
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<tr>
<td>Hepatic cirrhosis</td>
<td>β-Adrenergic blockers (eg, propranolol)</td>
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<tr>
<td>Pheochromocytoma</td>
<td>β-Adrenergic blockers (eg, propranolol)</td>
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<tr>
<td>Addison's disease</td>
<td>Phenoxybenzamine</td>
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<td>Bartter's syndrome</td>
<td>Phentolamine</td>
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<tr>
<td>Hormones</td>
<td>Nonsteroidal anti-inflammatory agents</td>
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<tr>
<td>Histamine</td>
<td>(eg, indomethacin)</td>
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<tr>
<td>Glucagon</td>
<td>α2-Agonists (centrally acting)</td>
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<tr>
<td>Glucocorticoids</td>
<td>Clonidine</td>
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<td>Estrogen</td>
<td>Guanabenz</td>
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<td>Catecholamines</td>
<td>Methylpapa</td>
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<tr>
<td>Anesthesia</td>
<td>Neuronal depleting agents</td>
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<tr>
<td>Acute ureteral obstruction</td>
<td>Reserpine</td>
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<td>Drugs</td>
<td>Guanethidine</td>
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<td>Oral contraceptives</td>
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<tr>
<td>Angiotensin antagonists (sarin, saralasin)</td>
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<td>Angiotensin-converting enzyme inhibitors</td>
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<td>Captopril</td>
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<td>Enalapril</td>
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<td>Vasodilators</td>
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<td>Nitroprusside</td>
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<td>Hydralazine</td>
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<td>Minoxidil</td>
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<td>Diuretics</td>
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### Other Imaging Techniques

Computed tomographic scanning can accurately evaluate renal thickness and contour, but the resolution with current equipment is unsatisfactory for evaluating renal artery stenosis. Computed tomographic scanning is less accurate for longitudinal (polar) measurements because of respiration and motion of the kidneys. Currently available magnetic resonance imaging equipment can provide accurate estimates of renal thickness but cannot provide reliable estimates of the severity of renal artery stenosis. Magnetic resonance contrast media are being developed for better visualization of both vessels and organs, and future technology may enable more physiologic evaluation of kidney function and flow. Ultrasound imaging provides accurate measurements of renal size, volume, and contour, but estimating intra-arterial flow abnormalities with the newer equipment is tedious and requires considerable expertise on the part of the technician or physician. Thus, current ultrasound imaging is of limited value as a noninvasive screening or diagnostic test for renovascular hypertension.

### Tests to Determine the Significance of a Renal Artery Lesion

Renovascular hypertension is mediated by increased angiotensin II and/or increased vascular responsiveness to angiotensin II. It is logical that tests involving the responsiveness of the renin-angiotensin system have been used to predict the response of blood pressure to surgical revascularization or to percutaneous transluminal renal angioplasty.

### Plasma Renin Activity (PRA)

Combined experience suggests that measurements of PRA are of limited value in predicting which patients with renal artery stenosis will benefit from surgery or percutaneous transluminal renal angioplasty (PTRA). The sensitivity and specificity of an elevated PRA is such that 43% of results are false-negative and 34% of results are false-positive (23). It has also been noted that as many as 15% of patients with essential hypertension may have an elevated PRA.

### RENAL VEIN RENIN RATIOS (RVRR)

A comparison of renin activity from the effluent venous blood of the suspected ischemic kidney to that of the contralateral kidney has been used to predict cure or improvement in hypertension. While combined data suggest that positive RVRR results can predict benefit from surgery in more than 90% of patients, the same data suggest that approximately 50% of patients with non-laterализing RVRR will still benefit from the surgery (26). A lack of standard patient preparation and sampling techniques has also made it difficult to compare data obtained from one center with data obtained from another center. In cases of bilateral disease, renin production may be high in both kidneys and, therefore, the RVRR will not have predictive value. When the renin-angiotensin system is not stimulated, a small variance in basal renin secretion may produce large ratios that are not clinically important.

### Renal to Systemic Renin Index (RSRI)

The RSRI is determined by subtracting systemic renin activity from that of the renal vein and dividing the remainder by the systemic renin activity. These calculations allow one to determine renin hypersecretion from the ischemic kidney and contralateral renin suppression (27, 28). Although RSRI represents an important refinement in interpretation of renin activity in patients having renovascular hypertension, appropriate caution is needed in applying these data rigidly to clinical decision-making.
The Captopril Test

Preliminary evidence suggests that captopril administration can enhance renin secretion from a stenotic kidney for RVRR or RSRI studies (29, 30). Broad clinical application will determine whether captopril administration will be superior to other stimulatory maneuvers, such as depleting sodium, administering loop diuretics, or placing patients in an upright position.

CLINICAL MANAGEMENT

The major objectives in the management of renovascular hypertension are to prevent complications of hypertension by controlling blood pressure and to prevent or slow the loss of renal function. Initial medical treatment of renovascular hypertension uses the same principles of therapy as treatment of essential hypertension. The availability of newer antihypertensive agents, particularly ACE inhibitors, has improved the ability to control renovascular hypertension.

Judging if a patient has improved after intervention with surgery, PTRA, or medical therapy depends on the quality and quantity of information available before and after intervention. Evaluation of blood pressure response both before and after intervention depends on a number of variables, including multiple readings, observer accuracy, and patient compliance with antihypertensive therapy. Monitoring changes in renal function likewise requires adequate and accurate measurements before and after intervention. Similar comments can be made regarding interpretation of baseline and follow-up roentgenogram studies.

The issue of medical vs surgical treatment or PTRA for renovascular hypertension has generated intense interest and discussion for many years. To date, no prospective randomized study has been published addressing the long-term benefits and risks of medical vs surgical therapy or PTRA. Modification of other risk factors for cardiovascular disease must also be addressed as well as pharmacologic control of blood pressure. Careful assessments of changes in renal size and/or renal function have proved better indicators than blood pressure measurements of progression of renal artery stenosis, and these assessments must be performed periodically. A careful search for and control of other factors that may accelerate atherosclerosis (hyperlipidemia, smoking, diabetes mellitus, and obesity) should be undertaken. The need for additional investigation and surgical intervention or PTRA should be considered in those individuals resistant or refractory to medical therapy. If renovascular hypertension is to be managed medically, the goal of therapy must be to control blood pressure (diastolic blood pressure <90 mm Hg). If normalized blood pressure cannot be achieved, surgical intervention or PTRA should be considered. Deterioration in renal function is, of course, also an indication for considering alternative therapy.

Factors that would favor surgical therapy for renovascular hypertension include hypertension refractory to medication, younger age, a general medical status suitable for surgical intervention, and a threat to renal function by progressive renal artery disease. In the National Cooperative Study, the major determinants of operative mortality were coronary artery disease, bilateral renovascular disease, azotemia, and the magnitude of the operation performed. Recent reports suggest that careful preoperative screening and correction of existing coronary or carotid occlusive lesions before renal revascularization can reduce operative morbidity and mortality (31, 32).

Surgical Revascularization

Bypass procedures using autologous or synthetic grafts are the most common means of renal revascularization for both atherosclerotic and fibroplastic stenoses (32). Autologous saphenous vein grafts are most commonly used and have advantages over synthetic materials because it is easier to manipulate these grafts to fashion difficult anastomoses. Endarterectomy is an appropriate mode of treatment for many proximal atherosclerotic renal artery stenoses. In some patients, severe atherosclerosis or previous operations performed on the abdominal aorta may preclude safe performance of aortorenal bypass, so alternate methods of revascularization have been used (30). A splenorenal bypass is appropriate for performing left-sided renal revascularization and, since the liver receives a dual vascular supply, the hepatorenal-saphenous vein bypass has become an alternative method of achieving right-sided renal revascularization in such patients. Since current surgical techniques aimed at both improving blood pressure and preserving renal function became available, nephrectomy is not commonly performed unless a kidney is severely atrophic.

Aortorenal bypass with synthetic materials is indicated only when autologous vascular grafts are not available or when the abdominal aorta is to be replaced concomitantly. The limitations of prosthetic grafts are their potential infectivity, some increased tendency to thrombosis in the early postoperative period, and technical difficulties in constructing small, segmental arterial anastomoses.

Newly developed microvascular techniques using a branch autologous vascular graft may permit successful revascularization in situ with aortorenal bypass. Lesions not amenable to standard, in situ reconstructions at times may be treated by temporary removal of the kidney and precise microsurgical repair of the diseased vessel.

Current surgical treatment of patients with renovascular hypertension has significantly lower morbidity and mortality than those reported in earlier studies. Differences in outcomes among recent studies usually reflect the most prevalent disease entity responsible for the secondary hypertension in that series. Pediatric patients with renovascular hypertension are the most likely to be cured after restoration of renal blood flow or primary nephrectomy, and operative mortality in this subgroup is unusual. In adults, hypertension as a consequence of fibromuscular lesions is more often surgically correctable than that associated with atherosclerotic renovascular disease and probably reflects a younger average age and absence of coexisting essential hypertension. Results for adults with focal atherosclerotic disease are comparable with results for adults who have fibromuscular lesions. Morbidity and mortality rates for adults with generalized atherosclerosis used to be higher. Recognition and treatment of coexisting extrarenal disease in this subgroup, particularly in patients with coronary or extracranial carotid artery disease, has reduced the hazards of renal artery revascularization. Although the risks in treating renovascular hypertension with overt generalized atherosclerosis are higher, surgical therapy should be pursued when patients do not respond to or cannot tolerate medical therapy or have documented deterioration in renal function associated with progressive renovascular disease. Revascularization to preserve kidney function is being undertaken in increasing numbers of patients with renovascular disease and normal or controlled blood pressure.

PTRA

Percutaneous transluminal renal angioplasty now provides a nonsurgical but invasive method of treating renal artery stenosis and possesses the advantages of local anesthesia, minimal patient morbidity, shorter hospital
stays, and lower costs. In renovascular hypertension associated with fibromuscular dysplasias, the overall technical success rate approximates 90%, with approximately 50% of patients meeting the criteria for cure from hypertension. In unilateral, nonostial atheromatous lesions, the technical success rate also approximates 90%, but the cure rate is lower at approximately 30%. In patients with bilateral atherosclerotic renal artery disease, with occluded renal arteries or ostial lesions, technical success rates are low, and complication rates are higher. In these patients, surgical revascularization would appear to be the preferred method of treatment. The major complications associated with PTRA are puncture-site hematomas and occlusion or dissection of the renal artery or one of its branches. When experienced physicians perform PTRAs, complications occur in fewer than 5% of cases. In the fibromuscular dysplasias, the restenosis rate is less than 5%, whereas restenosis occurs in 20% to 30%, or more, of atherosclerotic lesions. Many patients in whom restenosis develops can undergoing a second dilatation with good results.

In some medical centers, PTRA is attempted at the time of aortography, particularly for patients with fibromuscular lesions and nonostial atherosclerotic stenosis of the renal artery. In this situation, PTRA is performed without benefit of additional tests or procedures to determine the hemodynamic significance of stenosis. An immediate response of blood pressure following successful PTRA in itself confirms the significance of the stenosis.

MEDICAL TREATMENT OF RENOVASCULAR HYPERTENSION

Before the early 1970s, pharmacotherapy for renovascular hypertension was traditionally empirical and, in general, similar to that of essential hypertension. Nevertheless, antihypertensive drug therapy can control blood pressure in most patients with renovascular hypertension. It has been suggested that patients with fibrous dysplasia, being younger and having fewer cardiovascular complications, require lower dosages of medication than do patients with atherosclerosis. The availability of B-adrenergic blockers in the 1970s and the introduction of ACE inhibitors in more recent years have provided two classes of antihypertensive agents that are particularly efficacious because they can interfere with the renin-angiotensin-aldosterone axis.

The precise mechanism of action of B-blockers in the control of hypertension is not known; however, it appears that these agents are more effective in patients with elevated plasma renin activity than in those with low-renin hypertension (38). Administration of B-blockers is particularly effective in combination with administration of a diuretic and, occasionally, a vasodilating agent. The improved efficacy of B-blocker combinations appears to be the case, although there are no prospective, well-controlled studies clearly demonstrating better control of renovascular hypertension with administration of B-blockers than with administration of drugs used before their introduction. There is little evidence to suggest that administration of B-blockers in patients with preexisting renal disease results in a deterioration of renal function or carries the risk of irreversible renal failure. Kidney function should still be monitored carefully, and administration of the B-blocker discontinued if a decrease in kidney function, not otherwise explained, is noted.

Angiotensin-converting enzyme inhibitors have demonstrated particular efficacy used alone or with diuretics and/or adrenergic inhibitors, in treating renovascular hypertension (39-41). These agents appear to have a complex mechanism of action. In addition to blocking the conversion of angiotensin II, ACE inhibition also increases plasma concentrations of vasodilator bradykinins and prostaglandins, reduces sympathetic responsiveness, and may modify baroreceptor reflexes and increase urinary sodium excretion. Captopril administration lowers blood pressure by decreasing peripheral vascular resistance without a change in cardiac output or heart rate. The persistent blood pressure reduction seen with long-term administration of captopril has been noted in many patients, regardless of plasma renin activity.

In patients with a high degree of stenosis to a solitary kidney or bilateral renal artery stenosis, a significant, reversible increase in serum creatinine levels may be observed during captopril therapy (42, 43). The renal response to captopril therapy may also depend on the state of sodium balance, with a significant reduction in kidney function seen only when the patient's sodium intake is restricted. The reduction in kidney function has been observed whether or not a concomitant decrease in blood pressure occurs, suggesting an intraglomerular role of angiotensin II. High dosages of captopril have been associated with significant adverse effects, including nephrectopic range proteinuria with an associated membranous glomerulopathy, leukopenia, rash, and dysgeusia. A clinical syndrome suggesting an acute interstitial nephritis has also been reported.

Enalapril is a new converting-enzyme inhibitor that has a longer half-life, enabling once daily administration (44). Acute responses appear to be related to pretreatment plasma levels of renin and angiotensin II, whereas long-term administration of enalapril bears no relation to these plasma concentrations. Control of blood pressure with enalapril therapy in renovascular hypertension appears to be as good as that with captopril therapy. It is likely that acute hypotension or renal failure in patients with renal artery stenosis occurs with similar frequency with either drug.

Minoxidil, a potent vasodilator, has been shown to be useful in treating renovascular hypertension unresponsive to conventional antihypertensive therapy (45). Most patients taking minoxidil will require a B-blocker to attenuate the reflex tachycardia and a diuretic to counter the sodium retention. Interestingly, minoxidil therapy controls blood pressure in patients with renovascular hypertension despite stimulation of plasma renin activity, even when a B-blocker is used concurrently. Other classes of agents used in the conventional treatment of essential hypertension may also effectively control blood pressure in patients with renovascular hypertension. In view of the sodium and water retention associated with renovascular hypertension, diuretics are a necessary component of most successful treatment regimens. A thiazide diuretic is appropriate therapy for a patient with normal renal function, whereas therapy with a loop diuretic may be more appropriate for a patient with renovascular hypertension complicated by renal insufficiency or refractory edema. Limiting sodium intake to 70 to 100 mEq/L (70 to 100 mmol/L) daily will minimize the risks of hypokalemia and will enhance the antihypertensive effect of a diuretic. Currently, there is no reason to suppose that if two regimens lower blood pressure to the same degree, one is preferable, unless it is associated with fewer side effects, convenience to the patient, reduced frequency of drug administration, or lower cost.

The patient with severe renal artery stenosis and severe hypertension must be monitored with extreme care. Blood pressure control may critically reduce renal perfusion in the presence of severe renal artery stenosis and can accelerate loss of renal mass and function that might have been prevented by earlier intervention. Because blood pressure can be controlled with pharmacologic agents in most patients with renovascular hypertension, the role of medical therapy vs surgery or percutaneous transluminal angioplasty needs to be reevaluated. Unfortunately, there are no prospective,
Fig 3.—Algorithm: diagnosis and management of renovascular hypertension (RVH). PTRA indicates percutaneous transluminal renal angioplasty; HBP, high blood pressure; PRA, plasma renin activity; and IV-DSA, intravenous digital subtraction angiography.
randomized clinical trials that have addressed this issue, and treatment decisions remain individualized.

THERAPEUTIC DECISIONS

In patients with fibromuscular dysplasia, surgical revascularization or PTBA may be appropriate for those with moderate or severe hypertension, even though blood pressure can be controlled medically, particularly since these patients are younger and represent suitable surgical risks. Furthermore, the need for lifetime drug therapy makes surgery or PTBA even more attractive. Moreover, in some forms of fibromuscular dysplasia (peri-medial and intimal fibroplasia or medial hyperplasia), when the disease is bilateral, there may be progressive occlusion leading to decreased renal mass, progressive renal failure, and renal infarction in some patients. Conversely, in the most common form of fibromuscular dysplasia (medial fibroplasia), the lesion may be progressive, but the risk of renal function loss is minimal, and these patients may be considered suitable candidates for medical therapy. Blood pressure and renal function must be carefully monitored. Percutaneous transluminal renal angioplasty is being used increasingly in patients with fibromuscular dysplasias of the main renal artery and in selected patients with branch stenoses. Complications have been acceptably low, and the long-term results appear to be excellent after successful PTBA.

In the case of atherosomatous renovascular hypertension, the benefits of improved medical therapy may be even more evident. For this group of patients (60% to 70% of all renovascular hypertensives), one may be less confident about recommending surgery or PTBA when the functional significance of the lesion cannot be firmly established. These patients are also older, have more generalized vascular disease, and present a higher surgical risk. Moreover, atherosclerotic lesions are often not amenable to PTBA, and medical therapy is more readily accepted than it is in younger patients. There is, however, a significant risk of progressive renal failure from atherosclerotic occlusive disease, even if those patients with adequate blood pressure control, particularly when there is greater than 75% stenosis with bilateral disease or a solitary functioning kidney. Periodic assessment of individual kidney function is imperative. Even in the presence of bilateral, moderate, or severe stenosis, renal atrophy is often unilateral, and profound impairment of the function of one kidney may occur while estimates of overall renal function remain normal. Isotopic assessment of renal function is simple and noninvasive, and can provide valuable information regarding the function of individual kidneys.

Screening for and correcting existing coronary or cerebrovascular occlusive disease, avoiding bilateral simultaneous renal operations, and relying on methods of revascularization that obviate operation on a badly diseased aorta have significantly reduced surgical mortality in patients with atherosclerotic renovascular disease. Surgical therapy may not only be beneficial in terms of blood pressure control, but may also preserve renal function in a significant number of patients. Figure 3 provides an algorithm for evaluation of and decision-making for patients with suspected renovascular hypertension.

A prospective, randomized study is needed to evaluate the effectiveness of surgery, PTBA, and medical treatment, and to assess the value of techniques to detect renal artery stenosis and its functional significance. This special article represents the final report of a Working Group to the National High Blood Pressure Education Program, National Heart, Lung and Blood Institute, Bethesda, Maryland. Members of the Working Group included: Donald G. Vitt, M.D. (Chairman), Clarence E. Grim, M.D., Jerome G. Porush, M.D., Thomas A. Sos, M.D., and James C. Stanley, M.D.

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